

Supplemental Materials

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Acknowledgements

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FG loci

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Supplemental Figure Legends

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Conflicts of Interest and Disclaimer

Participating consortia and investigators

The data used in the current report were derived from published results from The Meta-Analyses of Glucose and Insulin-related traits Consortium (**MAGIC**)¹ and from unpublished meta-analyses from the African American Glucose and Insulin genetic Epidemiology (**AAGILE**) consortium. Only non-diabetic individuals were included in the trans-ethnic meta-analysis that combined data from MAGIC and AAGILE consortium. All data on participants of European ancestry (EA) were obtained from MAGIC (n = 51,750) while all data on participants of African ancestry (AA) were obtained from the AAGILE Consortium (n = 20,209). Cohorts that contributed data to the MAGIC consortium and names of the steering committee members are listed on the consortium website: <http://www.magicinvestigators.org/>.

The AAGILE consortium includes AA individuals from 16 cohorts. Key characteristics for each discovery and replication study sample are shown in **Table S1**. Investigators from AAGILE consortium are listed in the author list while those from the MAGIC consortium are shown below.

MAGIC investigator¹

Manning AK, Hivert MF, Scott RA, Grimsby JL, Bouatia-Naji N, Chen H, Rybin D, Liu CT, Bielak LF, Prokopenko I, Amin N, Barnes D, Cadby G, Hottenga JJ, Ingelsson E, Jackson AU, Johnson T, Kanoni S, Ladenvall C, Lagou V, Lahti J, Lecoeur C, Liu Y, Martinez-Larrad MT, Montasser ME, Navarro P, Perry JR, Rasmussen-Torvik LJ, Salo P, Sattar N, Shungin D, Strawbridge RJ, Tanaka T, van Duijn CM, An P, de Andrade M, Andrews JS, Aspelund T, Atalay M, Aulchenko Y, Balkau B, Bandinelli S, Beckmann JS, Beilby JP, Bellis C, Bergman RN, Blangero J, Boban M, Boehnke M, Boerwinkle E, Bonnycastle LL, Boomsma DI, Borecki IB, Böttcher Y, Bouchard C, Brunner E, Budimir D, Campbell H, Carlson O, Chines PS, Clarke R, Collins FS, Corbatón-Anchuelo A, Couper D, de Faire U, Dedoussis GV, Deloukas P, Dimitriou M, Egan JM, Eiriksdottir G, Erdos MR, Eriksson JG, Eury E, Ferrucci L, Ford I, Forouhi NG, Fox CS, Franzosi MG, Franks PW, Frayling TM, Froguel P, Galan P, de Geus E, Gigante B, Glazer NL, Goel A, Groop L, Gudnason V, Hallmans G, Hamsten A, Hansson O, Harris TB, Hayward C, Heath S, Hercberg S, Hicks AA, Hingorani A, Hofman A, Hui J, Hung J, Jarvelin MR, Jhun MA, Johnson PC, Jukema JW, Julia A, Kao WH, Kaprio J, Kardina SL, Keinanen-Kiukkaanniemi S, Kivimäki M, Kolcic I, Kovacs P, Kumari M, Kuusisto J, Kyvik KO, Laakso M, Lakka T, Lannfelt L, Lathrop GM, Launer LJ, Leander K, Li G, Lind L, Lindstrom J, Lobbens S, Loos RJ, Luan J, Lyssenko V, Mägi R, Magnusson PK, Marmot M, Meneton P, Mohlke KL, Mooser V, Morken MA, Miljkovic I, Narisu N, O'Connell J, Ong KK, Oostra BA, Palmer LJ, Palotie A, Pankow JS, Peden JF, Pedersen NL, Pehlic M, Peltonen L, Penninx B, Pericic M, Perola M, Perusse L, Peyser PA, Polasek O, Pramstaller PP, Province MA, Rääkkönen K, Rauramaa R, Rehnberg E, Rice K, Rotter JI, Rudan I, Ruukonen A, Saaristo T, Sabater-Lleal M, Salomaa V, Savage DB, Saxena R, Schwarz P, Seedorf U, Sennblad B, Serrano-Rios M, Shuldiner AR, Sijbrands EJ, Siscovick DS, Smit JH, Small KS, Smith NL, Smith AV, Stančáková A, Stirrups K, Stumvoll M, Sun YV, Swift AJ, Tönjes A, Tuomilehto J, Trompet S, Uitterlinden AG, Uusitupa M, Vikström M, Vitart V, Vohl MC, Voight BF, Vollenweider P, Waeber G, Waterworth DM, Watkins H, Wheeler E, Widen E, Wild SH, Willems SM, Willemsen G, Wilson JF, Witteman JC, Wright AF, Yaghootkar H, Zelenika D, Zemunik T, Zgaga L; DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium; Multiple Tissue Human Expression Resource (MUTHER) Consortium, Wareham NJ, McCarthy MI, Barroso I, Watanabe RM, Florez JC, Dupuis J, Meigs JB, Langenberg C.

Sources of data for pleiotropy studies

Consortia that contributed results for associations between fasting glucose or fasting insulin SNPs and insulin-related traits (i.e., hypertension, systolic and diastolic blood pressure, triglycerides, high density lipoprotein cholesterol, low density lipoprotein cholesterol, body mass index and waist-to-hip ratio-adjusted for BMI) are shown below:

1. Continental Origins and Genetic Epidemiology Network (COGENT) consortium²

The COGENT consortium provided association results for hypertension and for systolic and diastolic blood pressure.

2. Electronic Medical Records and Genomics Network (eMERGE)³

The eMERGE consortium provided triglyceride data from BioVU at Vanderbilt University Medical Center (<https://vict.vanderbilt.edu/pub/biovu/>) and triglyceride and blood pressure (hypertension and systolic and diastolic blood pressure) data from Mt. Sinai School of Medicine.

3. The National, Heart, Lung and Blood Institute's Candidate gene Association Resource (CARE)⁴

The CARE consortium contributed association results for high density lipoprotein cholesterol and low density lipoprotein cholesterol.

4. MEta-analysis of type 2 Diabetes in African Americans (MEDIA) Consortium⁵

The MEDIA consortium provided association results for type 2 diabetes.

5. African Ancestry Anthropometry Genetics (AAAG) Consortium^{6,7}

The AAAG consortium provided association results for body mass index and waist-hip-ratios.

Author contributions

The contributions of authors are summarized below:

Assembling and steering the consortium: AA, APM, BMP, CNR, CTL, DJC, DKA, DS, DWB, EB, EPB, IM, JBM, JCF, JD, JGW, JIR, JSP, LEW, LF, MAN, MAP, MMS, RJFL, SSR, YIC

Genotyping and data imputation: AA, EPB, GC, JAS, JIR, JY, KDT, LJRT, MAP, MF, MMS, MOG, RJFL, SLRK, TT, XG, YIC, YL

Phenotyping of the study participants: ANK, DS, EPB, JAP, JIR, JK, JMZ, MAP, MLB, PAP, RJFL, RK, SLRK, YIC, YL

Statistical analyses: AA, ABZ, AC, ADJ, AHZ, AJK, ALP, AMD, ARB, BEC, BP, CA, CDL, CTL, DC, DV, DS, DSE, DVR, DWB, EKK, EPB, ES, GC, JACD, JD, JDE, JH, JL, JL, JTZ, JY, KEN, KJG, KMR, LAL, LFB, LL, LLA, LRY, MAJ, MAP, MBS, MC, MCYN, MFK, MGH, MKE, ML, MPW, MRI, MS, NA, NF, NM, OG, PA, PAP, RAJ, RK, SL, SR, SRP, SS, ST, TBH, THM, TLE, TT, UN, WLL, WMC, WMC, WZ, XG, XL, XZ, YL, YL, YPF

SNP annotation: AMD, KJG, LL, JH, SR, KH

Drafting of the manuscript: AMD, APM, ASL, CTL, DS, DMB, DV, EKK, EPB, ES, JBM, JCF, JD, JGW, JH, JIR, KDT, KH, KJG, LL, LRY, MCYN, MD, MFH, MGH, ML, MOG, MMS, NM, PA, RJFL, RK, SR, SSR, WHLK, WMC, XG, XL, YIC, YL

Enhancing the manuscript for intellectual content: All authors

Approval of the final version: All authors

SNP annotation

Following trans-ethnic meta-analysis of data from **MAGIC** (EA participants) and the **AAGILE** consortium (AA participants), we identified 14 fasting glucose (FG) and 9 fasting insulin (FI) loci (**Table S5**) in which the number of SNPs in a locus or the size of the genomic region likely to harbor the causative SNP was reduced by at least 20%. For each of the SNPs in the narrowed region, referred to as the 99% credible set, we used HaploReg V2 to annotate their biological relevance. HaploReg provides useful annotation information for the SNP of interest as well as those within a user-specified LD. The fully operational web version is available at <http://www.broadinstitute.org/mammals/haploreg/haploreg.php>. HaploReg reports any evidence for regulatory chromatin marks, DNase I hypersensitivity sites (DHSI), transcription factor binding sites (TFBS), transcription factor binding motifs, or expression quantitative trait loci (eQTL) overlapping with each SNP of interest and thus gives mechanistic insights into how non-coding SNPs may lead to a given disease condition. Ward and Kellis provide more detailed information on HaploReg and its usage.⁸

After HaploReg we performed additional annotation manually using annotation resources in the public domain (i.e., [RegulomeDB](#), [ENCODE](#), [Islet Regulome](#) and [FANTOM](#)) to further characterize potential regulatory functions of the variants in the credible sets. Use of HaploReg together with manual annotation revealed whether a given SNP lies in a location with a histone mark suggestive of regulatory activity, a DHSI, TFBS, or if the SNP is in a gene expressed in a diabetes-relevant tissue, e.g., the liver or pancreas. In the case of histone marks we also evaluated whether the histone mark corresponds to an enhancer or promoter. Finally, we catalogued other traits with significant associations reported within the credible set from the NHGRI GWAS Catalog. Below we provide detailed information on the potential biological relevance of SNPs in each of the 14 FG and 9 FI loci that we annotated; the index SNP in EA indicated in parentheses.

1. FOXA2 (rs6048205)

- a. Credible set interval in hg18: chr20:22505099-22508971
- b. Credible set interval in hg19: chr20:22557099-22560971
- c. The region contains the 5' end of TCONS_00028636 (lincRNA)
 - i. Displays especially high expression in liver cell lines
 - ii. Is accompanied by moderate to high transcription levels (RNA-seq) only in HepG2 cell lines
 - iii. The EST BG655894 indicates expression in pancreatic Islets
- d. There are five broad and weak H3K4Me1 peaks in the region
 - i. Especially prominent in Embryonic stem cells
- e. There are 51 TFBSs in the region, all but 2 are expressed in liver cell lines
- f. The lead SNP is 20bp telomeric (p arm) to a DHSI (19/125) which is found in pancreatic islet cell lines
- g. The lead SNP sits inside 10 TFBSs
 - i. They are all found in liver cell lines
 - ii. Includes FOXA1 and FOXA2
- h. The RNA-seq information from the TFBSs in the region as well as the expression profile of the lincRNA indicate that the locus plays a role in the liver. The lead SNPs position in several binding sites may lead to a disruption in the binding of TFBSs.

2. GCK (rs4607517)

This credible set contained a single SNP; annotation overlap for the SNP can be found in Supplemental Table 5.

3. CRY2 (rs11605924)

- a. Credible set interval in hg18: chr11:45820718-45835568
- b. Credible set interval in hg19: chr11:45864142-45878992
- c. Contains 5' end of CRY2
- d. There is one NHGRI SNP
 - i. rs11605924 – fasting glucose traits
- e. There are 7 moderate to weak H3K4Me1 peaks in the region
- f. There are 3 weak and 1 strong H3K4Me3 peaks in the region
- g. There are 2 weak and 2 strong H3K27Ac peaks in the region
- h. The lead SNP is 1kbp upstream of a weak H3K4Me1 peak
 - i. DHSI (27) found in liver cell lines
 - ii. 9 TFBSs
- i. 5.6kbp upstream of weak H3K4Me1 and H3K27Ac peaks
 - i. DHSI (57) found in muscle and pancreatic islets
 - ii. 3TFBSs
- j. 1kbp downstream of a weak H3K4Me1 peak
 - i. DHSI (3) and (32)
- k. 3.8kbp downstream of dual H3K4me1, H3K4Me3, and H3K27Ac peaks
 - i. DHSI (111) and (125)
 - ii. 101 TFBSs
- l. 6.5kbp telomeric (p arm) to the SNP is a strong H3K4Me3 peak
- m. 8kbp telomeric to the SNP are weak H3K4Me1, H3K27Ac, H3M4Me3 peaks
 - i. DHSI (125)
 - ii. 49 TFBSs
- n. The lead SNP lies in the promoter region of CRY2, which explains its proximity to several H3K4Me1 peaks. Because CRY2 impacts metabolism, a polymorphism in the gene's promoters may alter the function.

4. KL (rs576674)

- a. Credible set interval in hg18: chr13:32209005-32701555
- b. Credible set interval in hg19: chr13:33311005-33803555
- c. Four genes in the region
 - i. 3' end of PDS5B
 - ii. KL
 - iii. STARD13
 - iv. TCONS_00021632 (lincRNA)
- d. Four NHGRI GWAS SNPs
 - i. rs2555603 – BMI
 - ii. (not related) rs2555603 – aneurysm
 - iii. (not related) rs642899 –behavioral disinhibition
 - iv. (not related) rs990324 – total ventricular volume
- e. There are 29 H3K4Me1 peaks throughout the region
- f. There are two H3K4Me3 peaks (weak)
- g. 15 H3K27Ac peaks throughout the region
- h. The lead SNP lies within a FOXA2 binding site found in liver cell lines
 - i. This is clustered near three other binding sites, all found in liver cell lines

- i. 10.5kbp telomeric (q arm) to a moderate H3K4Me1 peak and weak H3K4Me3 and H3K27Ac peaks
 - i. DHSI (66) found in muscle and pancreatic cells
 - ii. 6 TFBSs
- j. 4.6kbp upstream of a DHSI (26) in pancreatic islets
 - i. 12 TFBSs
- k. The lead SNP is in an intergenic region, and may serve as a bidirectional, distant regulator to both TCONS_00021632 and KL. The SNP may impact the binding of FOXA2 to its TFBS, and exert its effects primarily in the liver.

5. ADCY5 (rs11708067)

This credible set contained a single SNP; annotation overlap for the SNP can be found in Supplemental Table 5.

6. GCKR (rs780094)

This credible set contained a single SNP; annotation overlap for the SNP can be found in Supplemental Table 5.

7. PROX1 (rs340874)

- a. Credible set interval in hg18: chr1: 212212012-212230298
- b. Credible set interval in hg19: chr1:214145389-214163675
- c. Contains the 5'UTRs of PROX-AS1 and PROX1
- d. Exonic to the mRNA AK096113, overlaps PROX-AS1. Found in liver cell lines
- e. The 5'UTR of PROX-AS1 overlaps the mRNA AK096113, which comes from human liver cells
- f. There are 2 NHGRI SNPs in the region
 - i. rs2075423 – Type 2 Diabetes
 - ii. rs340874 – Fasting glucose traits
- g. There are 4 H3K4Me1 peaks throughout the region
- h. There is one weak and one strong H3K4Me3 peaks
- i. There are two H3K27Ac peaks
- j. The 5'UTR of PROX1 overlaps with a level of moderate transcription according to RNA-seq, especially strong in HepG2 cell lines (2.2kbp telomeric to (p arm) lead SNP)
 - i. There are also moderate H3K4Me1 and H3K27Ac peaks and a strong H3K4Me3 peak
 - ii. There is a DHSI (116/125) with 36 TFBSs (31 present in liver cells)
 - 1. TFBSs include FOXA1 and FOXA2
- k. 12.5kbp downstream, there is a large H3K4Me1 peak, with a DHSI (25/125) found in HSMC cells and one TFBS
- l. 8.2kbp downstream, there are strong H3K4Me1 dual peaks and small H3K37Ac peaks. There is a DHSI (27/125) and 9 TFBSs
- m. The lead SNP lies within an area of mild H3K4Me1 expression and several different DHSI and 41 TFBSs (31 expressed in liver cells)
 - i. The SNP is within two TFBSs: EZH2 and CTBP2
- n. The histone modifications are consistent with the location of the SNP within the promoter region of PROX1 and PROX1-AS1. This area may play an important role in the liver, as indicated by the tissue specificity of TFBSs, RNA-seq, and human mRNA.

8. DPYSL5 (rs1371614)

- a. Credible set interval in hg18: chr2: 26957635-27251700
- b. Credible set interval in hg19: chr2:27104131-27398196
- c. Contains 12 different genes
 - i. DPYSL5
 - ii. MAPRE3
 - iii. TMEM214
 - iv. OST4
 - v. KHK
 - vi. EMILIN1
 - vii. AGBL5
 - viii. CGREF1
 - ix. ABHD1
 - x. PREB
 - xi. C2orf53
 - xii. TCF23
- d. The 3'UTR of DYP5L5 contains high transcription levels, according to RNA-seq
- e. Two NHGRI SNPs
 - i. rs1371614 – Fasting glucose traits
 - ii. (not related) rs7588926 – Response to cytidine analogues
- f. There are 23 H3K4Me1 peaks throughout the region
- g. There are 12 H3K4Me3 peaks throughout the region
- h. There are 14 H3K27Ac peaks throughout the region
- i. The lead SNP lies with a DHS (3) and 2 TFBSs, FOXA1 and FOXA2, both found in liver cell lines
- j. 4kbp downstream of a small H3K4Me1 peak
 - i. DHS (26) found in liver, muscle, and pancreatic cell lines
 - ii. 23 TFBSs, all found in liver cell lines
- k. 13kbp upstream of an area of weak H3K4Me1 modification
 - i. DHS (113) and 13 TFBSs
- l. This is a larger transethnic region, with explains the large amount of genes with associated histone modifications. The SNP may impact the binding of FOXA1 and FOXA2, specifically in liver cells, which would affect liver metabolism.

9. IGF2BP2 (rs7651090)

- a. Credible set interval in hg18: chr3: 186750043-187067565
- b. Credible set interval in hg19: chr3:185267349-185584871
- c. Five genes in the region
 - i. LIPH
 - ii. SENP2
 - iii. IGF2BP2
 1. Human mRNA BC021290 indicates expression in pancreas
 - iv. C3orf65
 - v. TCONS_00006340 (lincRNA)
- d. Five NHGRI GWAS SNPs
 - i. (not related) rs720390 – height
 - ii. rs1374910 – Type 2 Diabetes
 - iii. rs6769511 – Type 2 Diabetes

- iv. rs1470579 – Type 2 Diabetes
- v. rs4402960 – Type 2 Diabetes
- e. There are 24 H3K4Me1 peaks throughout the region
- f. There are 3 H3K4Me3 peaks throughout the region
- g. There are 15 H3K27Ac peaks throughout the region
- h. The lead SNP is intronic to IGF2BP2
- i. 1.3kbp downstream of large H3K4Me1 and H3K27Ac peaks
 - i. DHSI (93) and 28 TFBSs
- j. 12kbp downstream of a DHSI (87)
 - i. 29 TFBSs
- k. 4.7kbp upstream of a moderate H3K4Me1 peak
 - i. DHSI (12)
- l. 13kbp upstream of an area of moderate H3K4Me1
 - i. DHSI (60) found in muscle and pancreatic cells
 - ii. 5 TFBSs
- m. The large Type 2 Diabetes SNP cloud indicates the importance of the region in that disease. The lead SNP is intronic to IGF2BP2, and 27 kbp from the nearest exon. Its role may be with the nearby putative promoter, located 1.3 kbp away. Further validation could show if this promoter is associated with IGF2BP2, or the downstream lincRNA TCONS_00006340.

10. CDKN2B (rs10811661)

- a. Credible set interval in hg18: chr9: 22118180-22124094
- b. Credible set interval in hg19: chr9:22128180-22134094
- c. No genes within the region
- d. 4 NHGRI GWAS SNPs
 - i. rs7020996 – Type 2 diabetes
 - ii. rs2383208 – Type 2 Diabetes
 - iii. rs10965250 – Type 2 Diabetes
 - iv. rs10811661 – Type 2 Diabetes
- e. There are three moderate, broad H3M4Me1 peak, especially prominent in blood vessel cells
 - i. 4kbp, 4.6kbp, and 5.4kbp telomeric (p arm) to the lead SNP
- f. 4.5kbp telomeric to the SNP, there is a DHSI (36/125) which is in HSMM and pancreatic islet cells. There are three TFBSs nearby, including FOXA2
- g. The entire region is intergenic and contains a large Type 2 Diabetes SNP cloud. This indicates the importance of the enhancer region, which overlaps a DHSI site with tissue specificity in diabetes-relevant tissues.

11. ADRA2A (rs10885122)

- a. Credible set interval in hg18: chr10: 112960941-113029657
- b. Credible set interval in hg19: chr10:112970951-113039667
- c. No genes in region
- d. Only histone modification is a very small H3K4Me1 peak between 113,005,278-113,007,774 only in HSMM cells
- e. There is a DHSI (8/125) in HSMM and PanIsletD.
- f. There are 9 TFBSs in the region, and 7 are present in liver cell lines
- g. **When using lift over, the lead SNP lies just outside the credible region** (113042093)

- h. This trans-ethnic region contains little biological information, being both intergenic and having little regulatory information. However, the information that is available shows tissue specificity to diabetes-relevant tissues, and may impact a genomic element not currently reported.

12. TCF7L2 (rs7903146)

- a. Credible set interval in hg18: chr10: 114742493-114778805
- b. Credible set interval in hg19: chr10:114752503-114788815
- c. The entire region is intronic to TCF7L2
 - i. Human mRNA FJ010174 indicates expression in pancreatic, hepatic, renal, muscle and adipose cells
- d. There are five NHGRI GWAS SNPs
 - i. rs12243326 – 2 hour glucose challenge
 - ii. (not related) rs7904519 – Breast cancer
 - iii. rs7903146 – Type 2 diabetes
 - iv. rs4506565 – fasting glucose traits/Type 2 Diabetes
 - v. rs7901695 – Type 2 diabetes
- e. There are 5 H3K4Me1 peaks (two strong, three weak)
 - i. The weak peaks are located 2.3kbp, 3.8kbp, and 5kbp downstream from the lead SNP
- f. 8.8kbp downstream, there is a DHSI (8/125) present in liver cell lines with 21 TFBSs, all present in liver cell lines
 - i. This coincides with a very strong peak of conservation
- g. The large Type 2 Diabetes SNP cloud, along with the tissue specificity information from the human mRNA, confirms the region's importance in diabetes. The SNP may play a role in the promoter regions and impact the transcription of TCF7L2, which is important in maintaining blood glucose levels. (<http://www.ncbi.nlm.nih.gov/gene/6934>)

13. FADS1 (rs174550)

- a. Credible set interval in hg18: chr11: 61307932-61366326
- b. Credible set interval in hg19: chr11:61551356-61609750
- c. There are five genes in the region
 - i. MYRF
 - ii. FEN1
 - 1. EST CA868349 indicating expression in pancreas
 - iii. TMEM258
 - iv. FADS1
 - v. FADS2
 - 1. EST BP237803 indicating expression in liver
- d. There are 20 NHGRI GWAS SNPs
 - i. rs174541 – metabolite levels
 - ii. rs4246215 – platelet counts, phospholipid levels
 - iii. rs174538 – blood metabolite levels
 - iv. rs102275 – blood cholesterol/metabolite levels, metabolic syndrome
 - v. (not related) rs174537 – colorectal cancer
 - vi. rs174556 – blood metabolite levels
 - vii. rs174555 – blood fatty acid levels

- viii. rs174550 – fasting glucose related traits
- ix. rs174548 – blood metabolite levels
- x. rs174547 – metabolic traits
- xi. rs174546 – metabolic syndrome, cholesterol
- xii. rs174578 – blood metabolite levels
- xiii. rs2727271 – blood metabolite levels
- xiv. rs2727270 – fatty acid levels
- xv. (not related) rs174583 – response to statins
- xvi. (not related) rs174577 – P wave duration
- xvii. rs174574 – phospholipid levels
- xviii. rs1535 – metabolic syndromw
- xix. (not related) rs174570 – glyated hemoglobin levels
- xx. rs968567 – blood metabolite levels
- e. Seven H3K27Ac peaks
 - i. Two are associated with H3K4Me1 peaks
- f. There are three H3KeMe3 peaks, all associated with H3K27Ac peaks
- g. There are eleven H3K4Me1 peaks, seven are associated with H3K27Ac peaks
- h. The lead SNP is intronic to FADS1
- i. The lead SNP is inside of a H3K4Me1 peak
- j. 12kbp upstream are strong H3K4Me3 and H3K27Ac peaks
 - i. associated with several DHSI (55,117,124,125,14). The 14/125 DHSI is in both hepatocytes and pancreatic cells. There are over 150 associated TFBSs
 - ii. On either side of this region are H3K4Me1 peaks
- k. 3.9kbp upstream of H3K4Me1 and K3K17Ac peaks
 - i. DHSI (12) found in pancreatic islet cells
 - ii. 42 TFBSs
- l. 11kbp telomeric (q arm) to H3K4Me3 and H3K27Ac peaks
 - i. DHSI (125) and (116)
 - ii. 87 TFBSs
- m. This region contains an expansive SNP cloud, which strengthens the case for the importance of the region in Type 2 Diabetes. Furthermore, several of the genes in the region are associated with metabolism and cholesterol, including FADS1 and FADS2. The location of the lead SNP within a promoter region may impact the transcription of these elements.

14. DGKB-TMEM195 (rs2191349)

- a. Credible set interval in hg18: chr7: 14888532-15032137
- b. Credible set interval in hg19: chr7:14922007-15065612
- c. Contains the 5' end of DGKB
- d. Contains 3 NHGRI SNPs
 - i. rs10244051 – metabolic traits
 - ii. rs2191349 – fasting glucose related traits
 - iii. rs6947830 – metabolic syndrome
- e. There are three small H3K4Me1 peaks
 - i. 8.7kbp telomeric (p arm) there is a DHSI (104) with HSMM, HepG2, and PanIslets cell lines. There are 16 TFBSs
- f. This transethnic region is mostly intergenic, with few biological elements. However, the presence of a SNP cloud indicates the importance of this region to Type 2 diabetes. The

SNP cloud is clustered around a small H3K4Me1 peak, which may be involved in distant regulation.

15. ARL15 (rs4865796)

- a. Credible set interval in hg18: chr5: 53059217-53557802
- b. Credible set interval in hg19: chr5:53023460-53522045
- c. There are two genes in the region
 - i. TCONS_I2_00022897 (lincRNA)
 - ii. 3' end of ARL15
 1. EST AV660016 indicating expression in liver
- d. There are 5 NHGRI SNPs in the region
 - i. rs4311394 – adiponectin levels
 - ii. rs6450176 – adiponectin levels/cholesterol
 - iii. (not related) rs273218 – migraine
 - iv. rs702634 – Type 2 diabetes
 - v. (not related) rs255758 – rheumatoid arthritis
- e. There are 14 H3K4Me1 peaks
 - i. There is one small peak located 1.5kbp downstream of the SNP
 - ii. 7kbp upstream there is a small peak, associated with a DHSI (42) present in HepG2 Cells and 7 TFBSs
- f. There are 3 H3K17Ac peaks, each corresponding to a H3K4Me1 peak
- g. There are numerous DHSI and TFBS throughout the region, as well as low-levels of transcription according to RNA-seq
- h. The lead SNP is located near a promoter region intronic to ARL15. While this may regulate the gene, which is shown to have tissue specificity to the liver and play a role in glucose levels via adiponectin (PMID: 20011104), it may also impact regulation of the downstream lincRNA TCONS_I2_00022897.

16. PPP1R3B (rs4841132)

This credible set contained a single SNP (rs1461729); annotation overlap for the SNP can be found in Supplemental Table 5.

17. COBLL1-GRB14 (rs7607980)

- a. Credible set interval in hg18: chr2: 165214970-165266498
- b. Credible set interval in hg19: chr2:165506724-165558252
- c. There are two genes in the region
 - i. 3' end of COBLL1
 1. EST CB270545 indicates expression in adipose tissue
 - ii. TCONS_00004484 (lincRNA)
 1. Increased expression in liver and adrenal tissue.
- d. Five NHGRI GWAS SNPs
 - i. rs10195252: Triglycerides
 - ii. rs13389219: Waist hip ratio
 - iii. (not related) rs6717858: sexual dimorphism is anthropometric traits

- iv. rs12328675: cholesterol
 - v. rs7607980: fasting insulin traits
- e. Between 165,536,302-165,558,065 (coinciding with COBLL1), there is moderate to high transcription according to RNA-seq
 - i. This is especially prominent in HepG2 cells
- f. 1.3kbp downstream, there is a DHSI (5/125) present in HepG2 cells, with 25 TFBSs (17 present in liver cells)
- g. 3.1kbp upstream, there is a DHSI (32) present in HSMM, PANC-1, and HepG2, associated with 7 TFBSs (all in liver cells)
- h. There is a moderate H3K4Me1 peak and small H3K27Ac peak in the region
- i. This trans-ethnic region shows several instances of tissue specificity in liver tissue, including information from TFBSs, DHSI, and lncRNA expression profiles. The lead SNP is exonic to COBLL1, which plays a role in cholesterol levels (PubMed: 17903299). This variant may impact the function of this gene.

18. IRS1 (rs2943634)

- a. Credible set interval in hg18: chr2: 226735108-226872748
- b. Credible set interval in hg19: chr2:227026864-227164504
- c. There are three genes in the region
 - i. TCONS_I2_00015614 (lncRNA) – especially prominent in thyroid
 - ii. TCONS_00003502 (lncRNA)
 - iii. TCONS_00004599 (lncRNA)
- d. There are seven NHGRI GWAS SNPs
 - i. rs2972146 – triglycerides/HDL cholesterol
 - ii. rs2943641 – Type 2 Diabetes
 - iii. rs2943650 – adiposity
 - iv. rs1515110 – adiponectin levels
 - v. rs2972146 – triglycerides/HDL cholesterol
 - vi. (not related) rs2943636 - sexual dimorphism is anthropometric traits
 - vii. rs2943634 – fasting insulin traits
- e. There are five H3K4Me1 peaks
 - i. 12.7kbp centromeric (q arm) – especially prominent in HSMM cell lines
 - ii. 10kbp telomeric – especially prominent in HSMM cell lines
- f. There are three H3K27Ac peaks, each coinciding with a H3K4Me1 peak
 - i. 12.7kbp centromeric (q arm) – especially prominent in HSMM cell lines
 - ii. 10kbp telomeric – especially prominent in HSMM cell lines
- g. 12.7kbp centromeric is a DHSI (21) with 9 TFBS (all in liver cells)
- h. 10kbp telomeric are two DHSIs with 27 TFBSs
 - i. This region contains only non-coding SNPs, highlighting their importance in metabolic disorders. The SNP cloud resides in an intergenic area of the region, with relatively few genomic features. However, the genomic features that are present display tissue specificity to Type 2 Diabetes relevant tissues. Further validation could uncover if this area serves as a distant regulator to another genomic area involved in Type 2 Diabetes.

19. GCKR (rs780094)

This credible set contained a single SNP; annotation overlap for the SNP can be found in Supplemental Table 5.

20. ANKRD55-MAP3K1 (rs459193)

- a. Credible set interval in hg18: chr5: 55595454-56092481
- b. Credible set interval in hg19: chr5:55559697-56056724
- c. There are five genes in the region
 - i. TCONS_00009667 (lncRNA)
 - ii. TCONS_00010339 (lncRNA) – especially prominent in kidney and adrenal
 - iii. TCONS_00009669 (lncRNA) – especially prominent in kidney and adrenal
 - iv. TCONS_00010343 (lncRNA) – especially prominent in kidney and adrenal
 1. 3' end located less than 1kbp from lead SNP
 - v. TCONS_00010346 (lncRNA)
- d. There are 11 NHGRI GWAS SNPs
 - i. rs9686661 – triglycerides
 - ii. (not related) rs11743303 - sexual dimorphism is anthropometric traits
 - iii. rs6867983 – waist circumference/triglycerides
 - iv. rs30360 – fasting insulin/insulin resistance
 - v. (not related) rs456867 – urate levels
 - vi. (not related) rs1020388 – Celiac's disease
 - vii. (not related) rs889312 – breast cancer
 - viii. (not related) rs16886181 – breast cancer
 - ix. (not related) rs16886165 – breast cancer
 - x. (not related) rs16886034 – breast cancer
 - xi. (not related) rs16886113 – breast cancer
- e. There are approximately 28 H3K4Me1 peaks
- f. The region has 1 H3K4Me3 peak
- g. There are seven H3K27Ac peaks, each coinciding with a H3K4Me1 peak
- h. 6kbp centromeric (q arm) is an area of high conservation and transcription according to RNA-seq. While there is no gene, histone mod, or TFBS corresponding to this region, there are 41 ESTs
- i. 9kb centromeric there is a H3K4Me1 peak. There is a DHSI (41) with 10 TFBSs
 - i. The DHSI is present in HSMMtube and PanIsletD cell lines
- j. 3.1kbp centromeric is a DHSI (6) present in HepG2 cells. There are 6 TFBSs, all present in liver cell lines
- k. 5.5 kbp telomeric is a H3K4Me1 peak. There is a DHSI (48) with 11 TFBSs.
 - i. The DHSI is present in HSMM and HepG2 cell lines
- l. 15 kbp telomeric is a broad H3K4Me1 peak. This encompasses several DHSI and TFBSs
- m. This region contains numerous lncRNA and regulatory elements, further emphasizing their importance. The tissue specificity of these elements in Type 2 Diabetes tissues, such as liver and muscle tissue, indicates that these features may be playing a role in the metabolic disorder. Further validation could be done to identify the specific targets of these areas.

21. FAM13A (rs3822072)

- a. Credible set interval in hg18: chr4: 89840095-90083469
- b. Credible set interval in hg19: chr4:89621072-89864446
- c. Contains two genes
 - i. 3' end of HERC3
 - ii. FAM13A
 1. The entire region of the gene shows transcription levels particularly prominent in HepG2 cell lines
- d. There are two NHGRI GWAS SNPs
 - i. (not related) rs2609255 – lung disease

- ii. rs3822072 – HDL cholesterol
- e. The region has 15 H3K4Me1 peaks
- f. There are 2 H3K4Me3 peaks (each coinciding with an Me3 peak)
- g. There are 6 H3K27Ac peaks (each coinciding with an Me3 peak)
- h. The lead SNP is intronic to FAM13A, is within a DHSI (4) and a TFBS (GATA3)
- i. 3.3kbp upstream there are peaks for each form of histone modification.
 - i. DHSI (119) and approximately 70 TFBSs
- j. 9kbp downstream is a DHSI (17) with 11 TFBSs, all present in liver cells
- k. The lead SNP in this region resides in the promoter region of the short isoform FAM13A, and may impact its rate of transcription. The tissue-specificity of the RNA-seq and TFBSs to the liver indicates where this effect may occur.

22. UHRF1BP1 (rs4646949)

- a. Credible set interval in hg18: chr6: 34872900-35090036
- b. Credible set interval in hg19: chr6:34764922-34982058
- c. Contains three genes
 - i. 3' end of UHRF1BP1
 - ii. TAF11
 - iii. 5' end of ANKS1A
- d. There are 6 NHGRI GWAS SNPs
 - i. (not related) rs3734266 – lupus
 - ii. (not related) rs2140418 – alcoholism
 - iii. (not related) rs1535001 – lupus
 - iv. (not related) rs847845 – lung cancer
 - v. (not related) rs12205331 – CAD
 - vi. rs4646949 – fasting insulin traits
- e. There are 18 H3K4Me1 peaks
- f. There is one H3K4Me3 peak
- g. There are eight H3K27Ac peaks
- h. The lead SNP is inside an area of high transcription according to RNA-seq and in between the short isoform of UHRF1BP1 and TAF11, but intronic to the long isoform of UHRF1BP1
- i. 1kbp telomeric (p arm) is a small H3K4Me1 peak
 - i. DHSI (1) with 6TFBSs
- j. 12kbp telomeric are strong H3K4Me1 and H3K27Ac peaks
 - i. DHSI (33) In HSMM and PanIsletD cell lines
 - ii. 33 TFBSs, with 32 in blood tissue
- k. 10kbp centromeric are strong H3K4Me3 and H3K27Ac peaks, and a moderate H3K3Me1 peak
 - i. There are several DHSIs (35,20,125,110)
 - ii. Over 100 TFBSs
- l. The lead SNP resides near the 3' end of two different genes, which explains its high rate of transcription. However, the small H3K4Me1 peak where the lead SNP resides may be a distant regulator of the downstream target ANKS1A, which has been previously identified in an obesity and Type 2 diabetes study (PMCID: PMC3364960).

23. PPARG (rs17036328)

- a. Credible set interval in hg18: chr3: 12311507-12371955
- b. Credible set interval in hg19: chr3:12336507-12396955
- c. The entire region is intronic to PPARG
- d. There are 2 NHGRI GWAS SNPs

- i. (not related) rs11128603 - PAI-1 levels
 - ii. rs1801282 – Fasting glucose and Type 2 Diabetes
- e. The region has only one strong H3K4Me1 peak, and six other weak peaks
- f. There are 3 weak H3K27Ac peaks, each coinciding with a Me1 peak
- g. The lead SNP is 3kbp downstream of the strong H3K4Me1 peak and a weak Me3 peak
 - i. There is a DHSI (67) found in muscle and pancreatic cell lines
 - ii. There are 17 TFBSs
- h. 1.7kbp Upstream of a DHSI (51) found in muscle and pancreatic cell lines. There are 27 TFBSs
- i. 4.4 kbp upstream of a DHSI (40) found in HepG2 and HSMM cell lines
 - i. There are 24 TFBSs
- j. While the region is intronic to the long isoform of PPARG, the lead SNP is 2.7kbp upstream of the 5' end of the short isoform. The nearby promotor signals, DHSI, and TFBSs may be involved in the regulation of this isoform. Genetic variations impacting PPARG may increase the risk for Type 2 Diabetes (PubMed: 15797964, PubMed 15592662, PubMed: 12882888).

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Conflict of Interest and Disclaimer

Conflicts of Interest

BMP serves on the DSMB of a clinical trial for the device manufacturer Zoll LifeCor and on the Steering Committee for the Yale Open Data Access Project funded by Johnson & Johnson. DV is a consultant for Consumable Science, Inc. JRK holds the ownership of stock in Pfizer, Inc, and Gilead Sciences, Inc.

Disclaimer

The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.

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FG loci

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Supplemental Figure Legends

Figure S1.

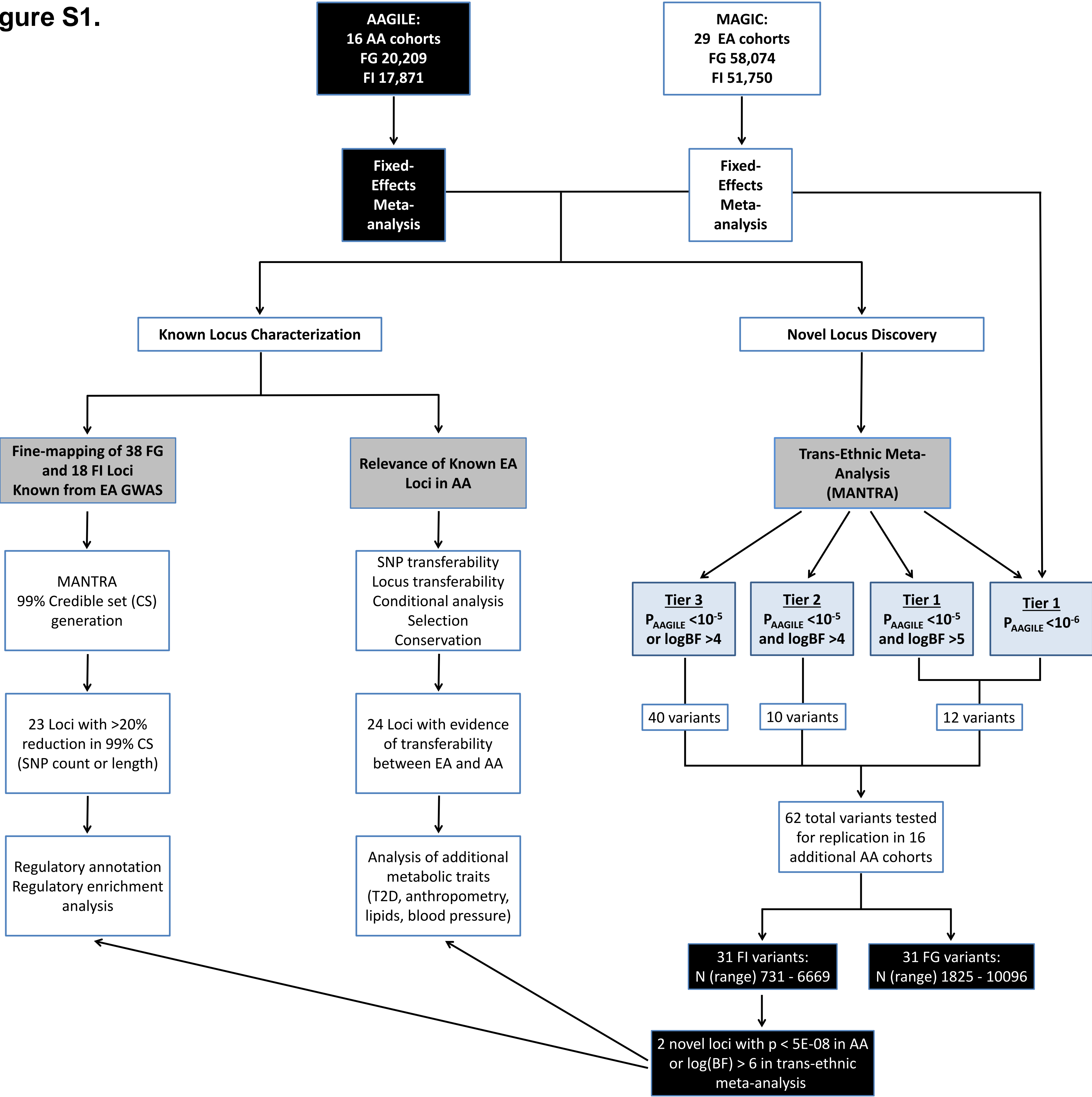


Figure S2.

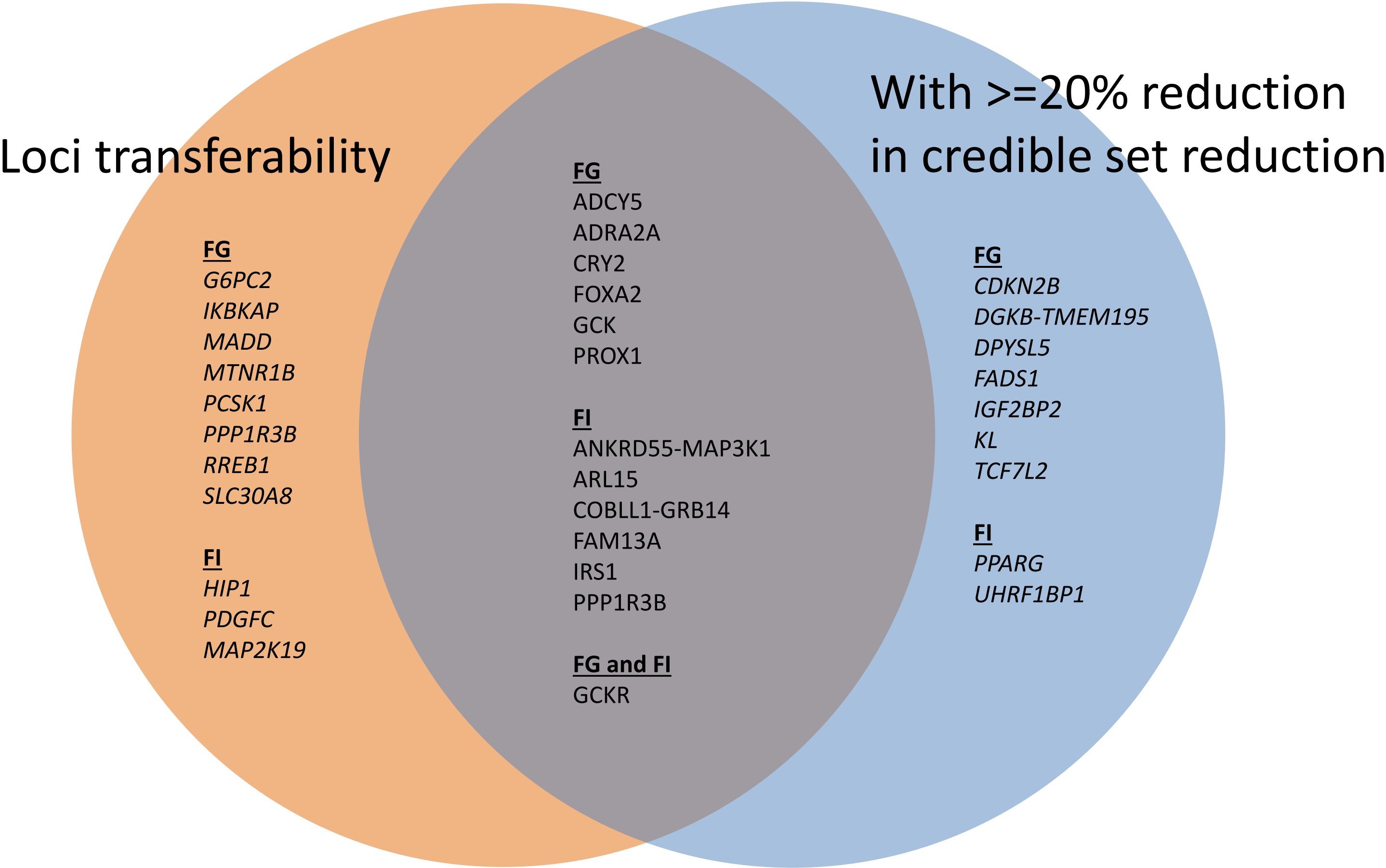
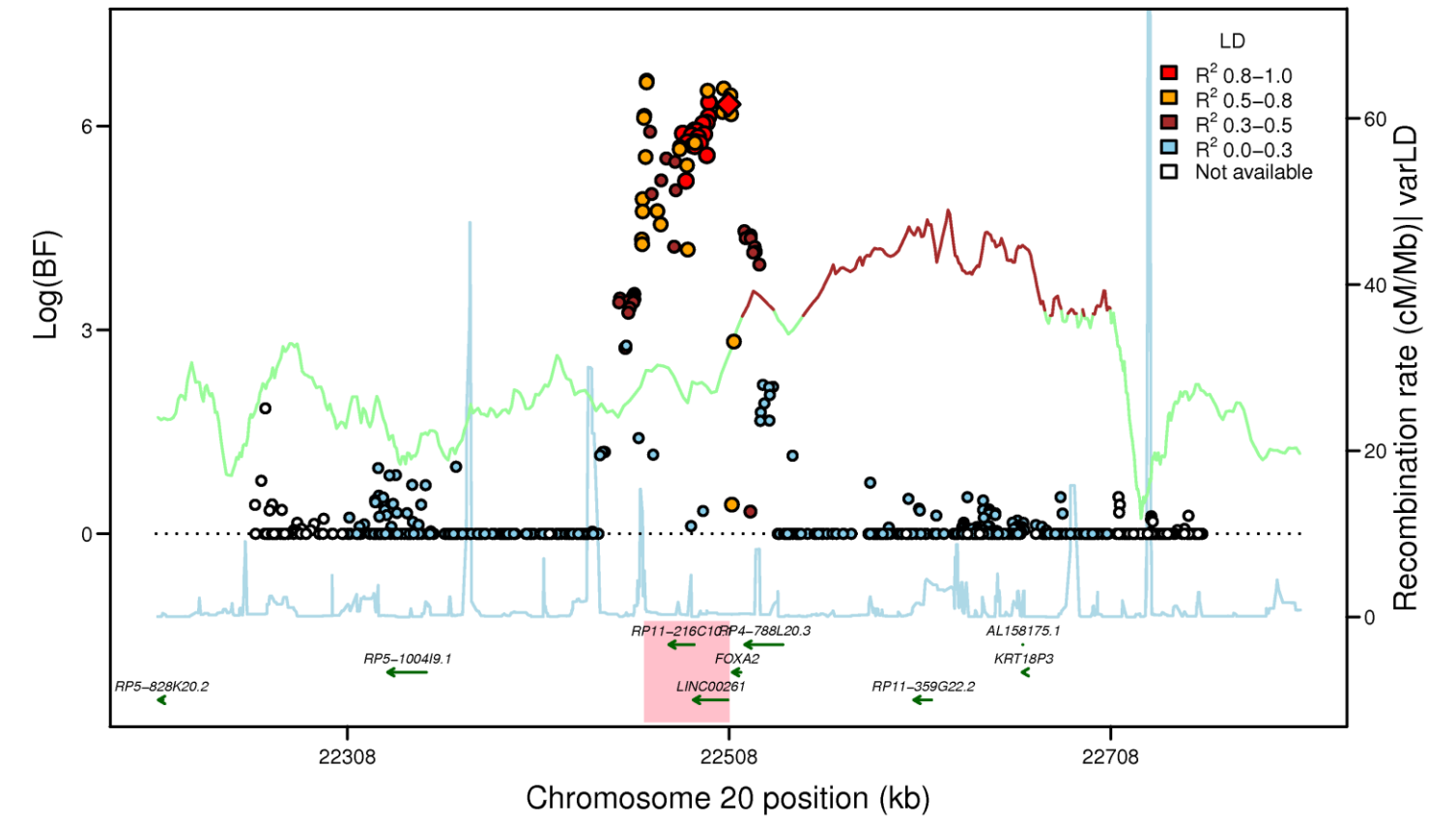
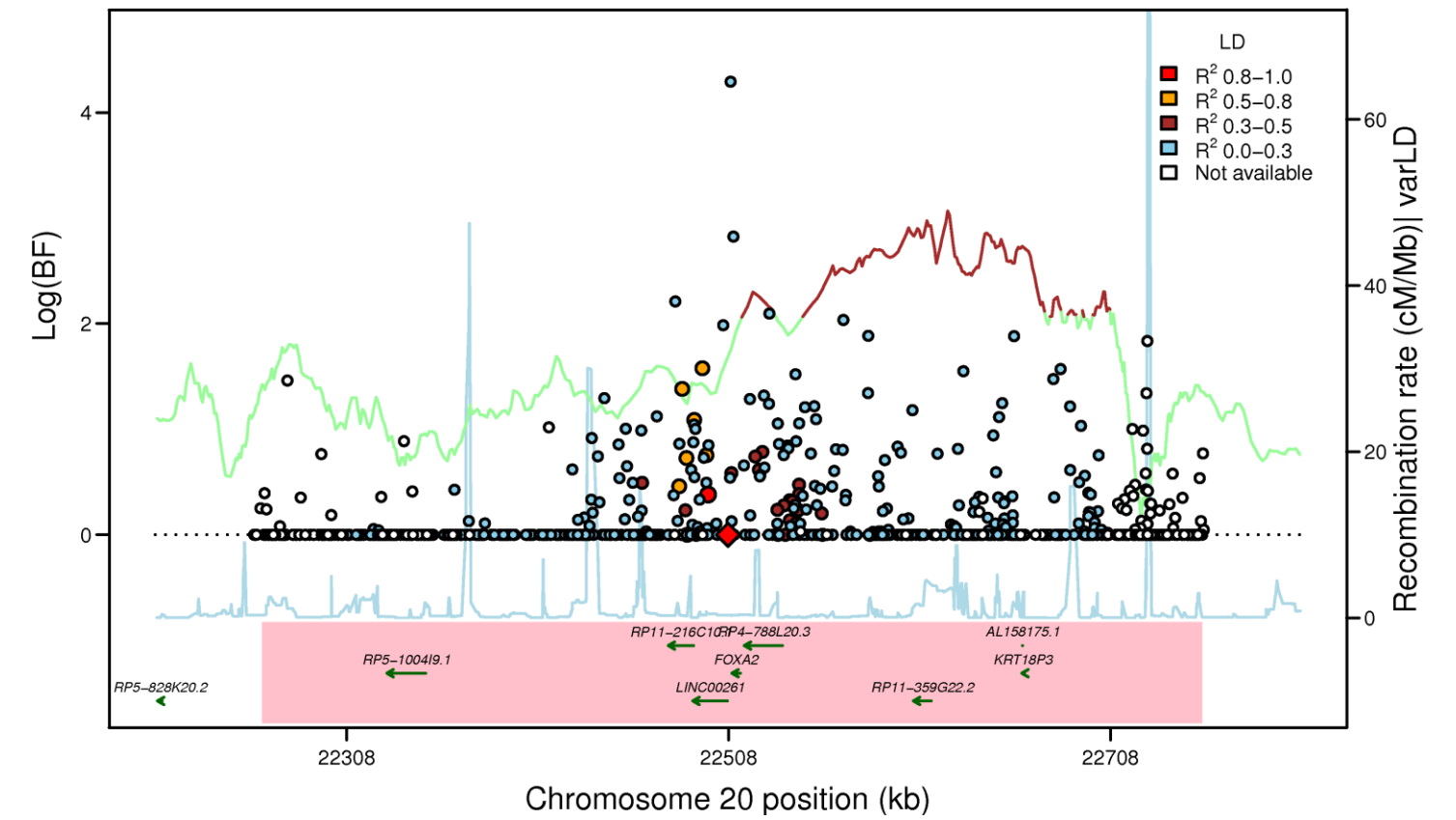


Figure S3A

FOXA2: rs6048205 (FG EA_MANTRA, LD: HapMap2 CEU)



FOXA2: rs6048205 (FG AA_MANTRA, LD: HapMap2 YRI)



FOXA2: rs6048205 (FG TE_MANTRA, LD: HapMap2 YRI)

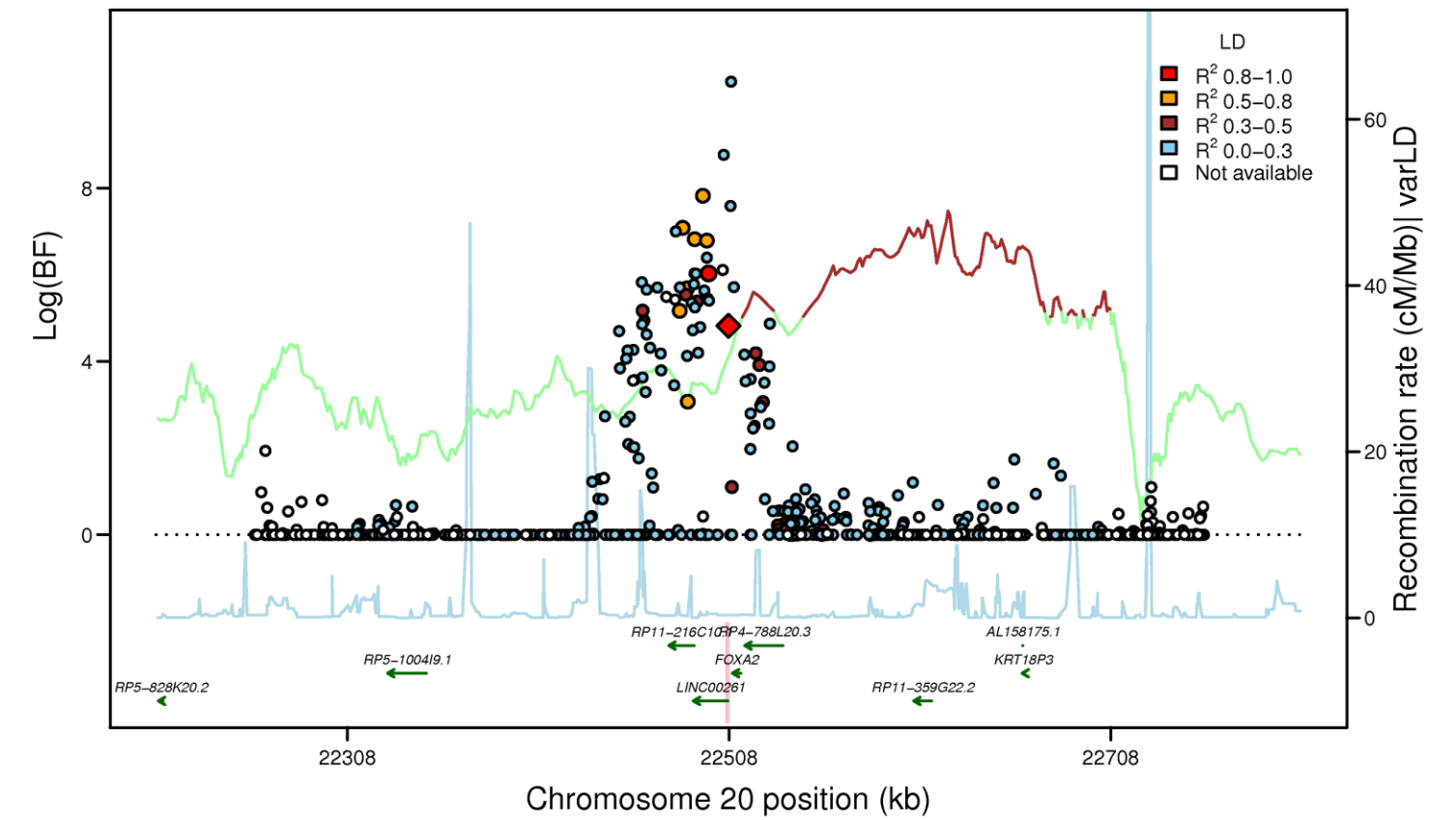
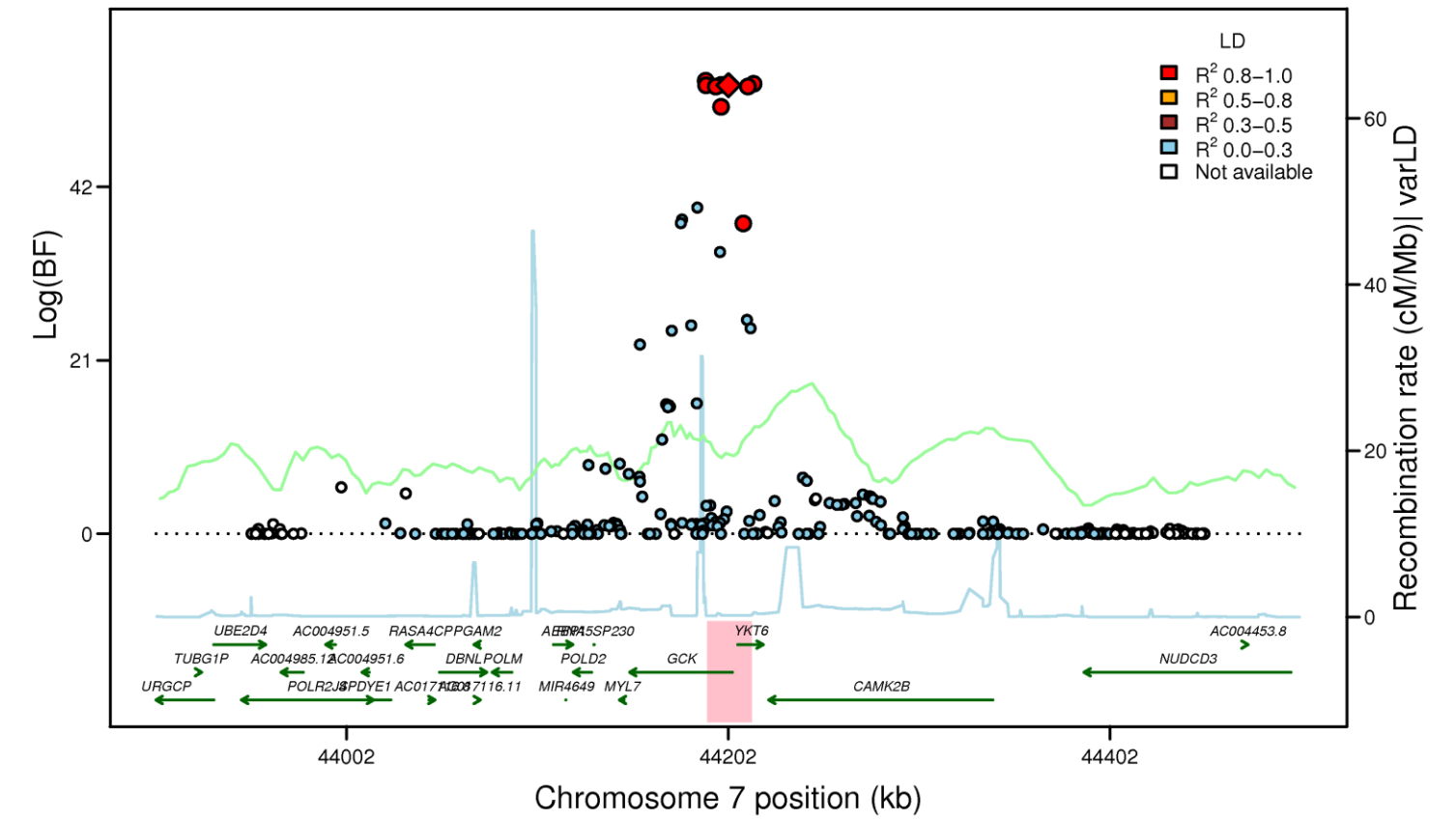
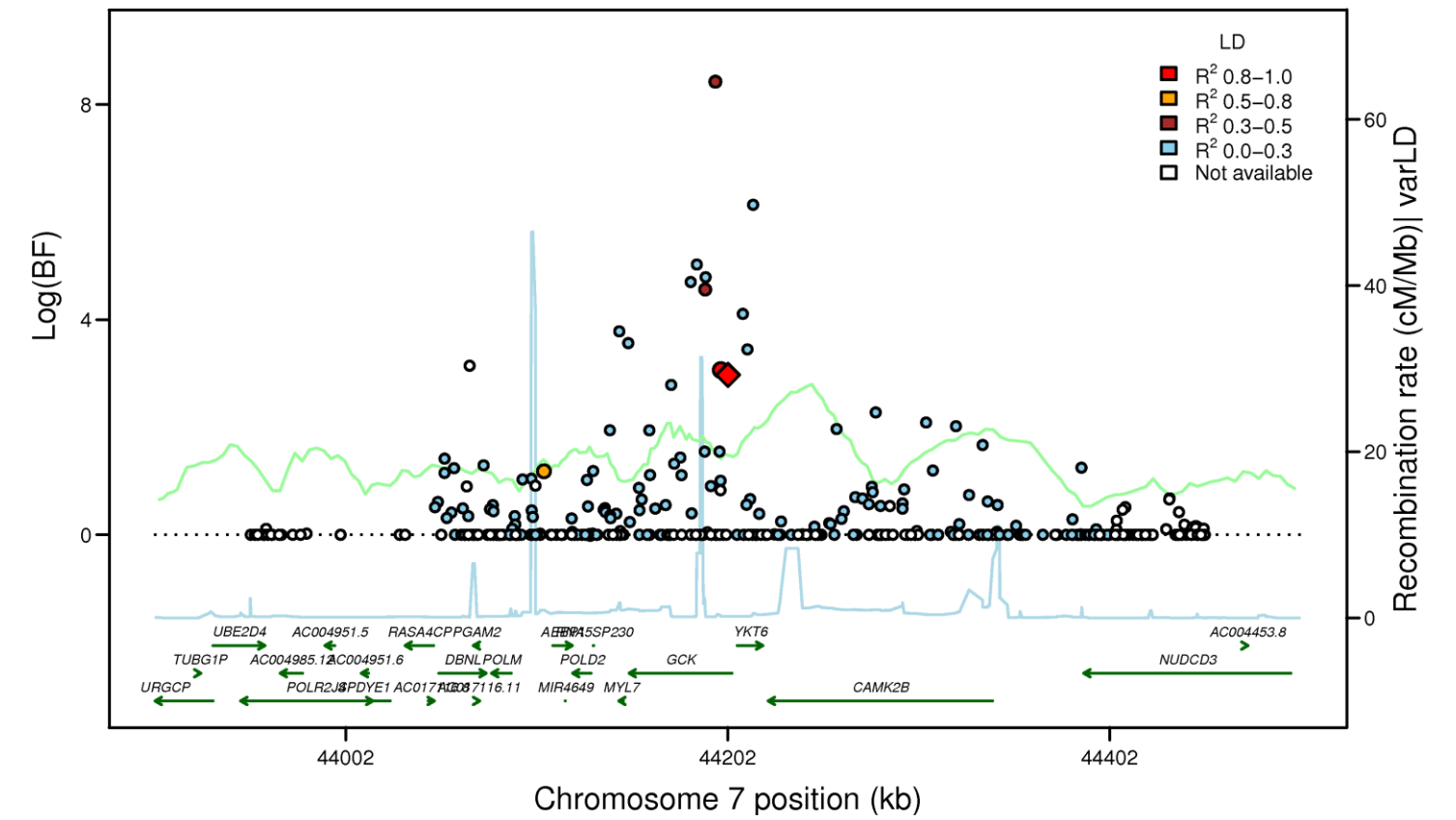


Figure S3B

GCK: rs4607517 (FG EA_MANTRA, LD: HapMap2 CEU)



GCK: rs4607517 (FG AA_MANTRA, LD: HapMap2 YRI)



GCK: rs4607517 (FG TE_MANTRA, LD: HapMap2 YRI)

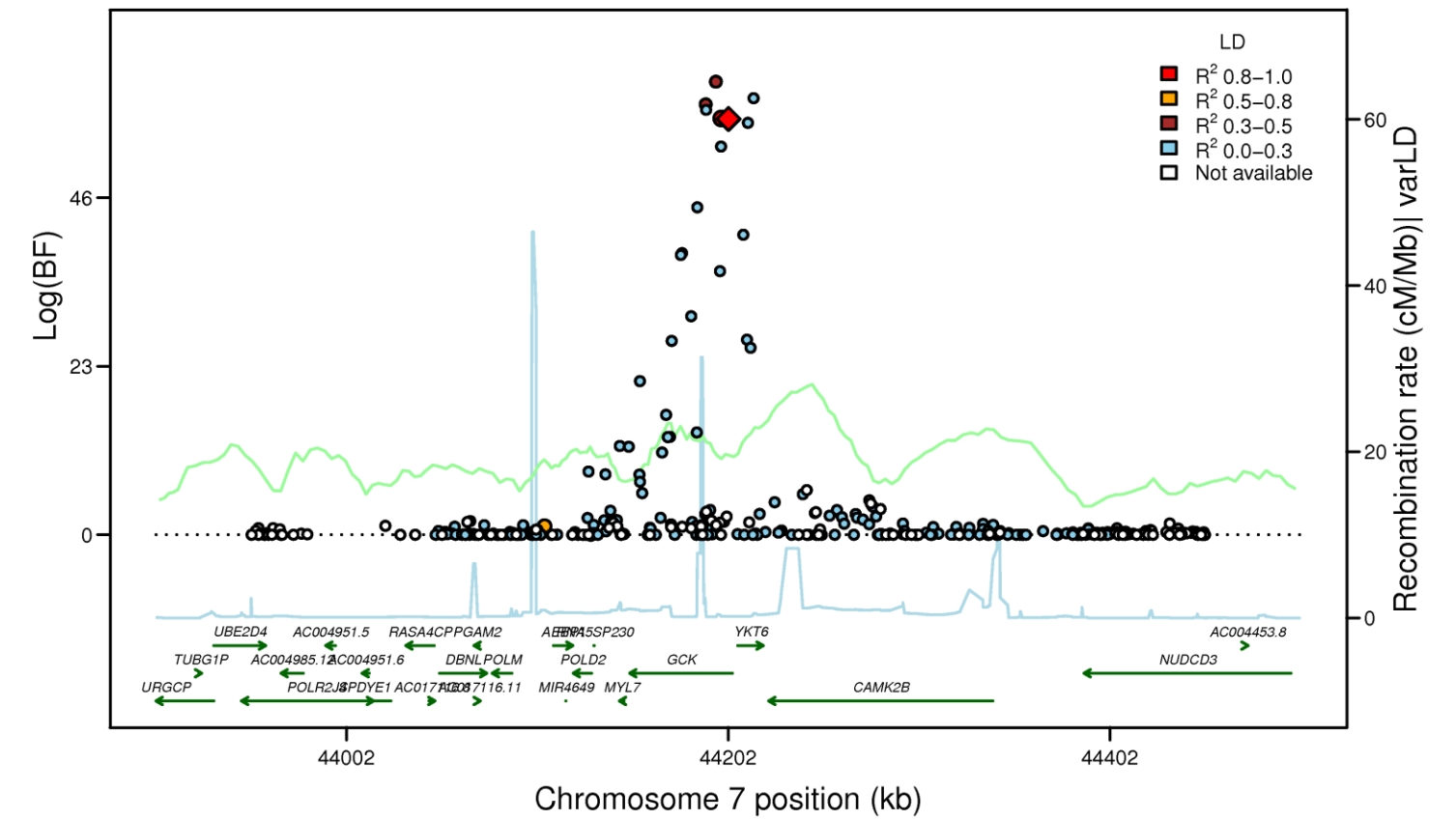
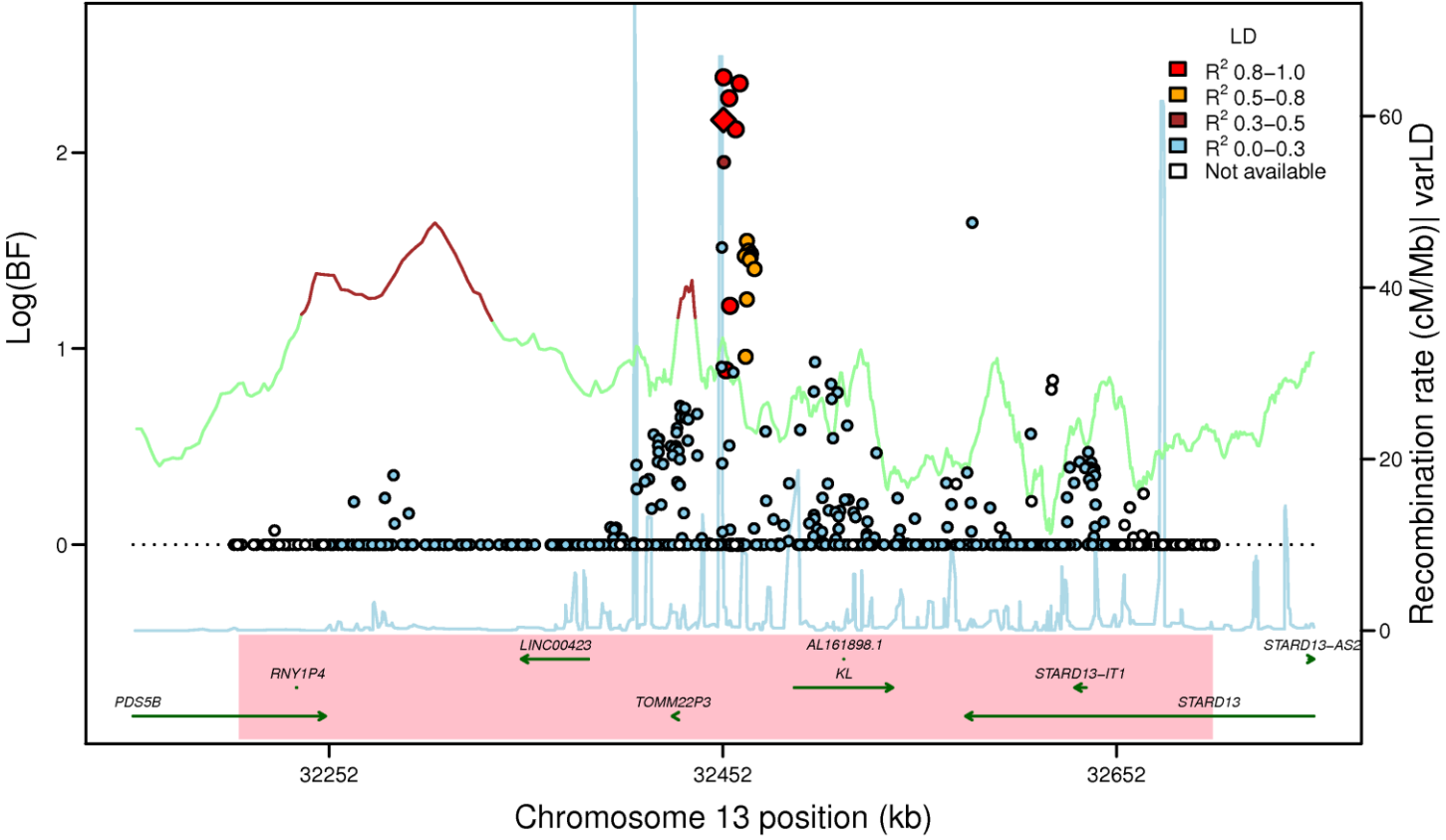
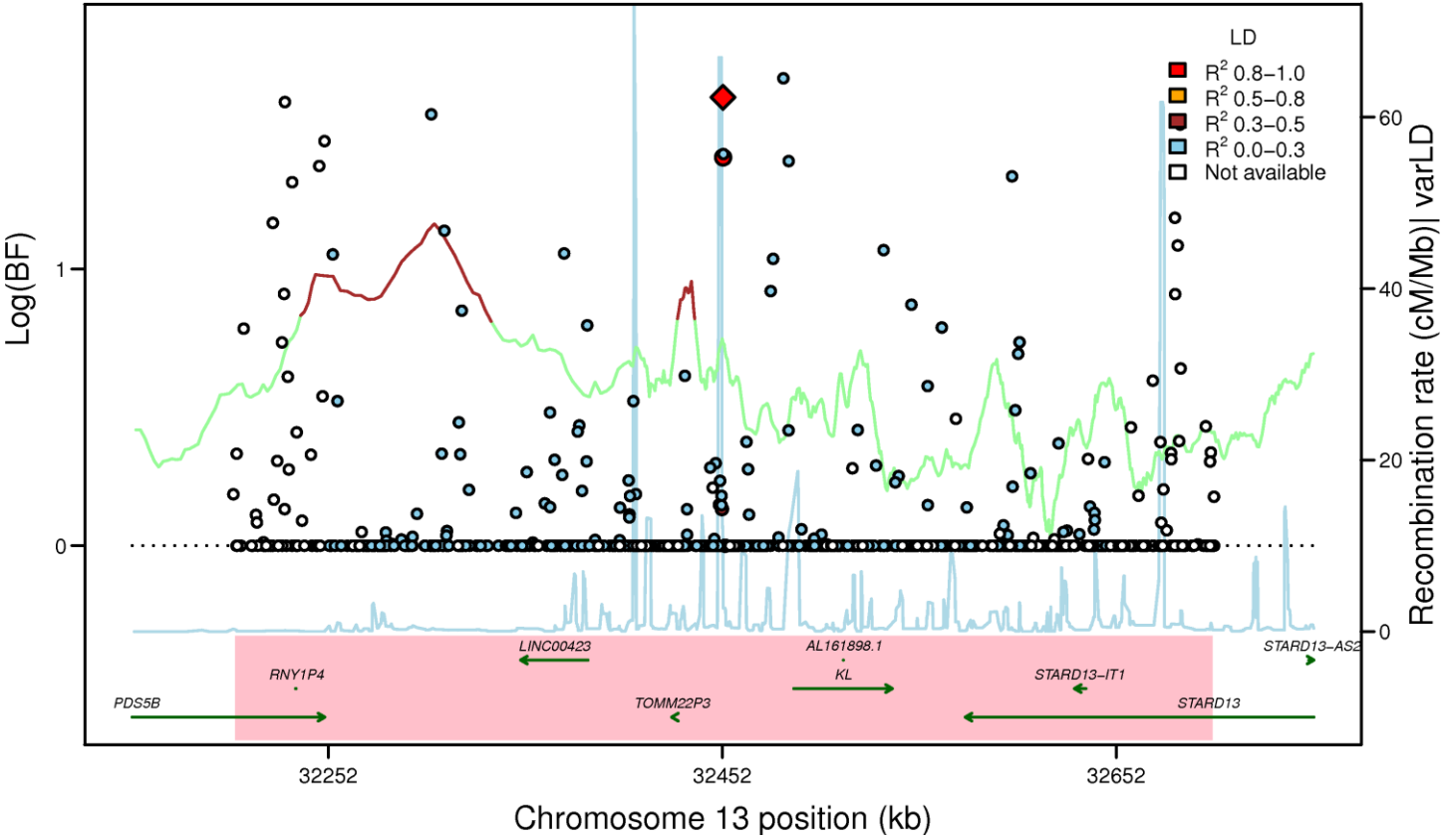


Figure S3C

KL: rs576674 (FG EA_MANTRA, LD: HapMap2 CEU)



KL: rs576674 (FG AA_MANTRA, LD: HapMap2 YRI)



KL: rs576674 (FG TE_MANTRA, LD: HapMap2 YRI)

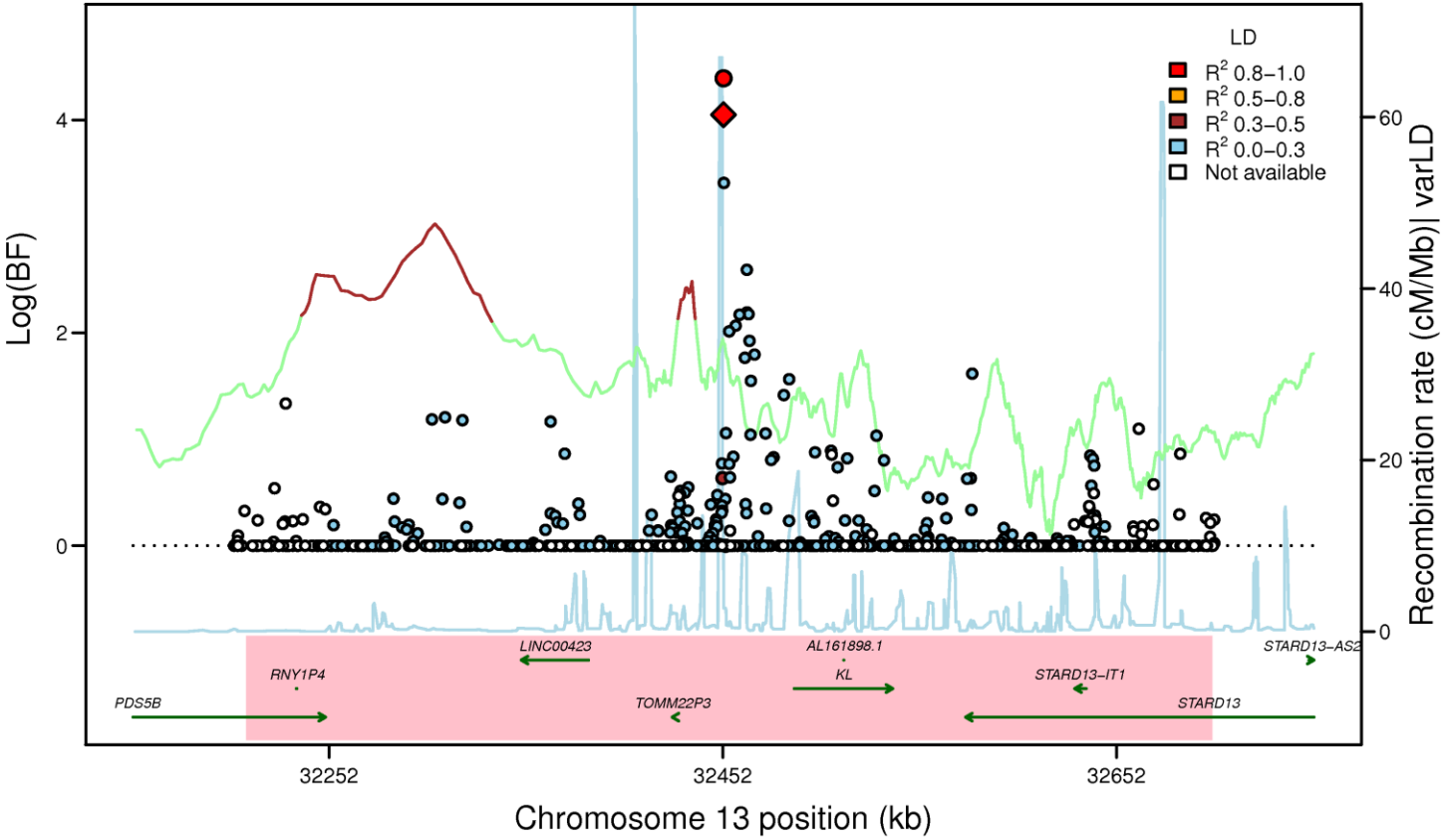
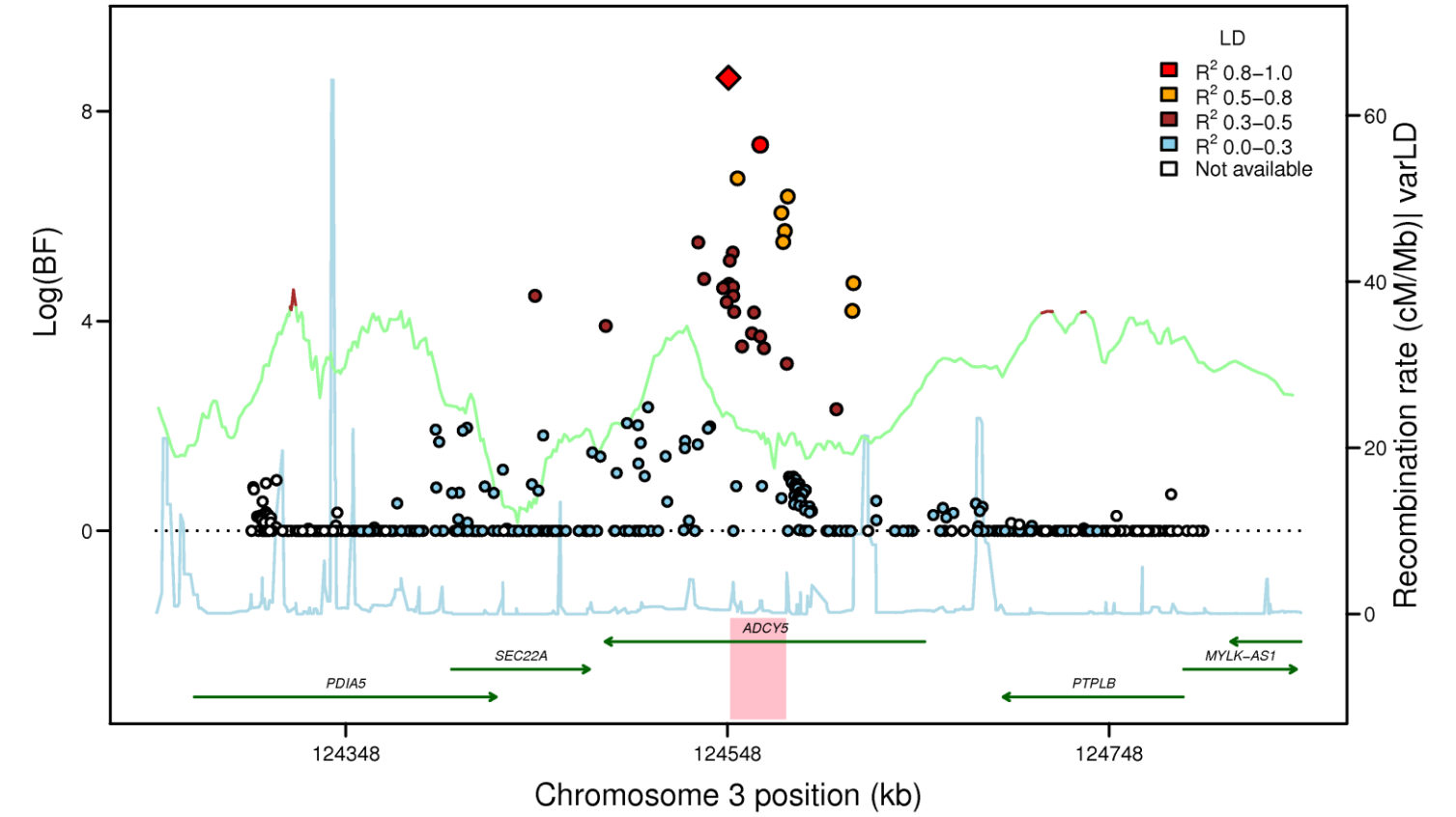
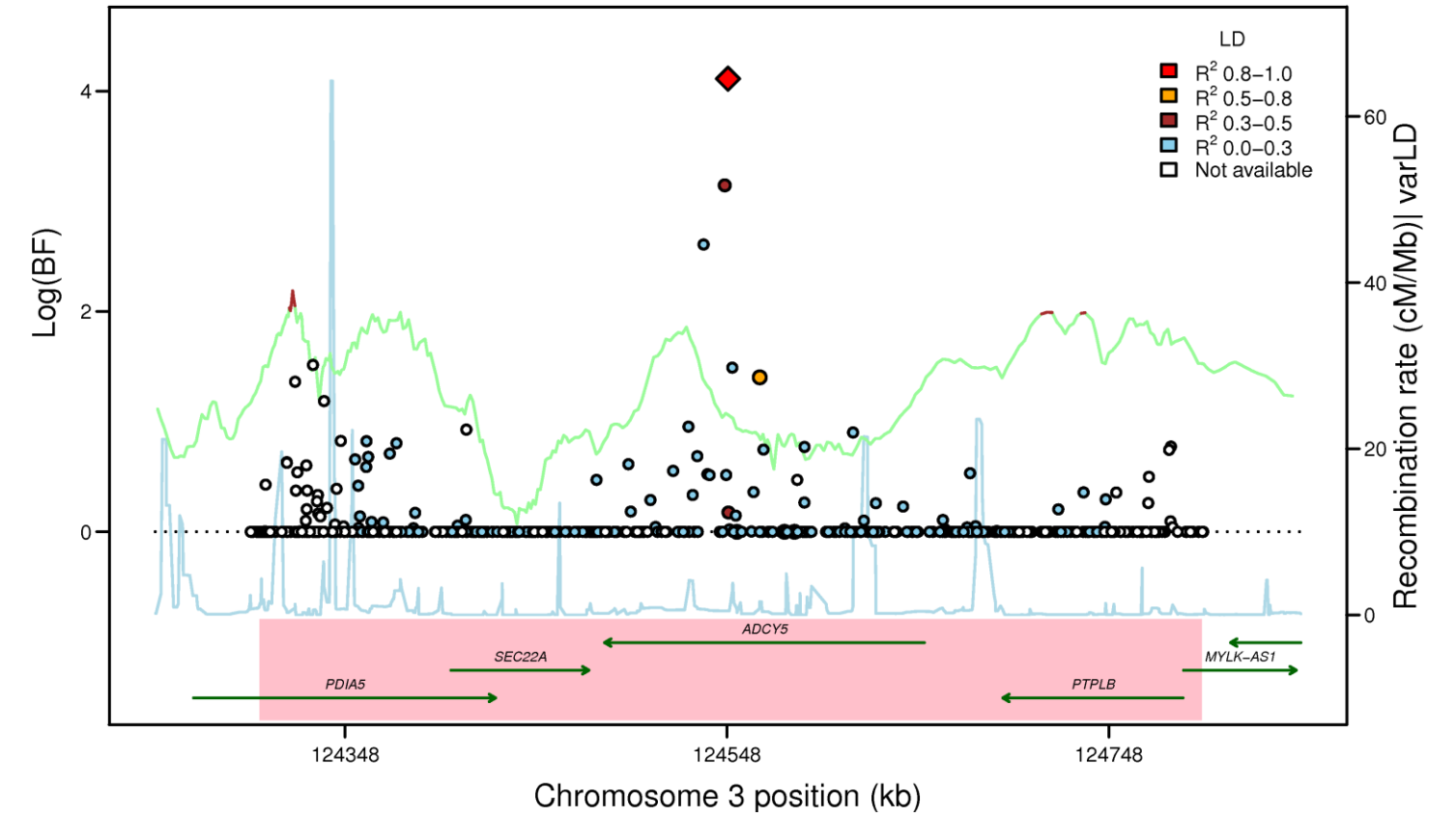


Figure S3D

ADCY5: rs11708067 (FG EA_MANTRA, LD: HapMap2 CEU)



ADCY5: rs11708067 (FG AA_MANTRA, LD: HapMap2 YRI)



ADCY5: rs11708067 (FG TE_MANTRA, LD: HapMap2 YRI)

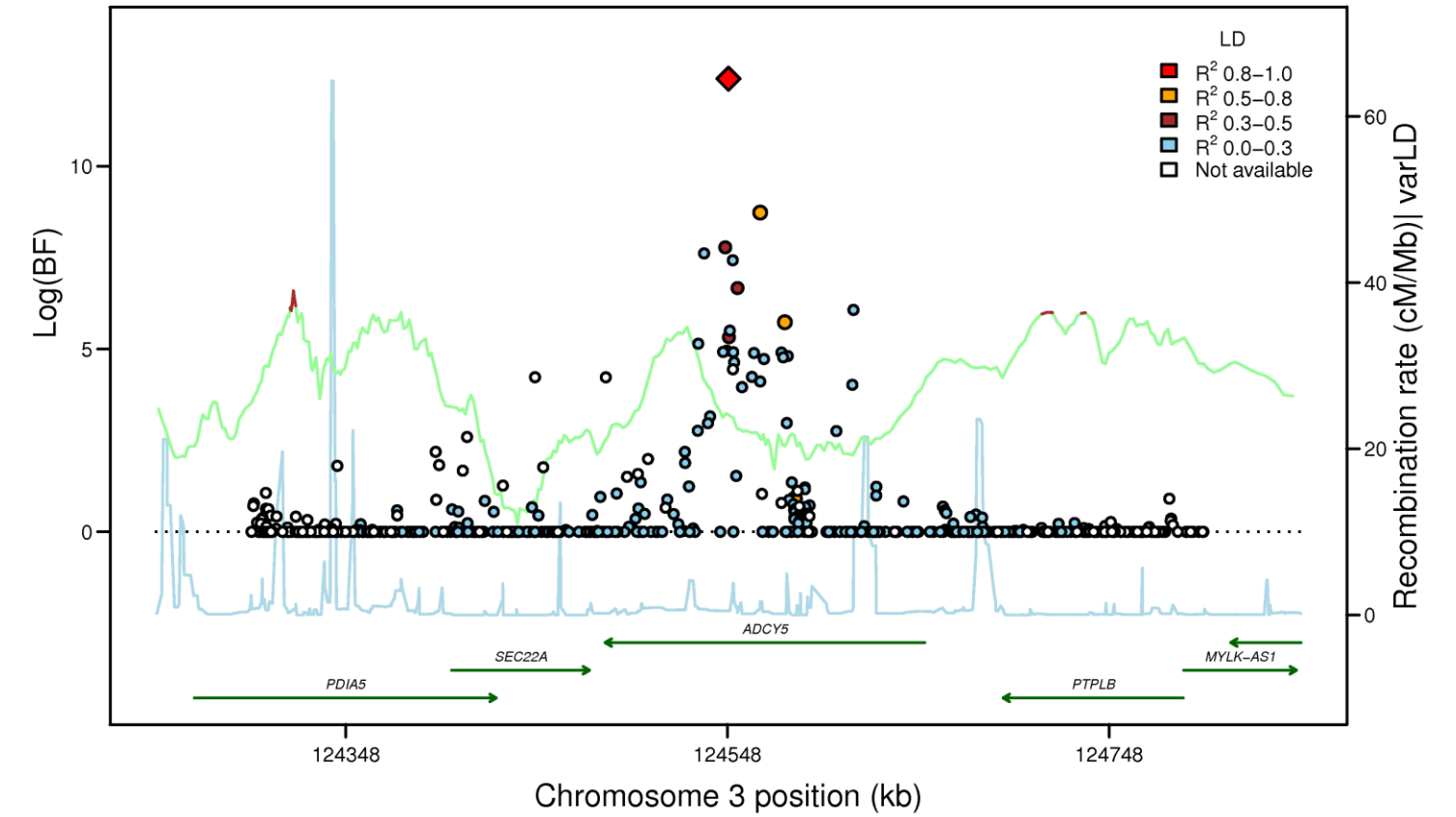
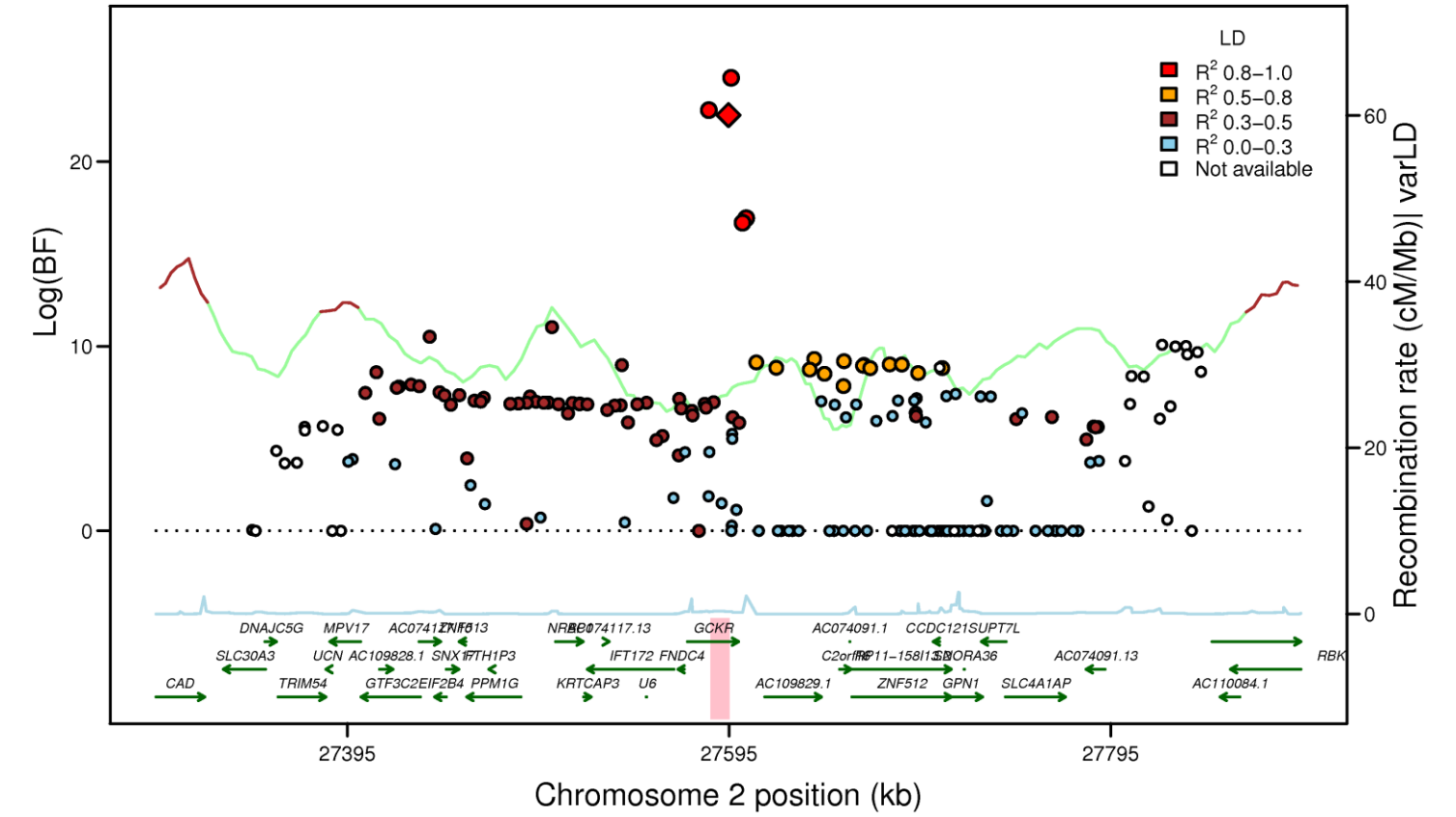
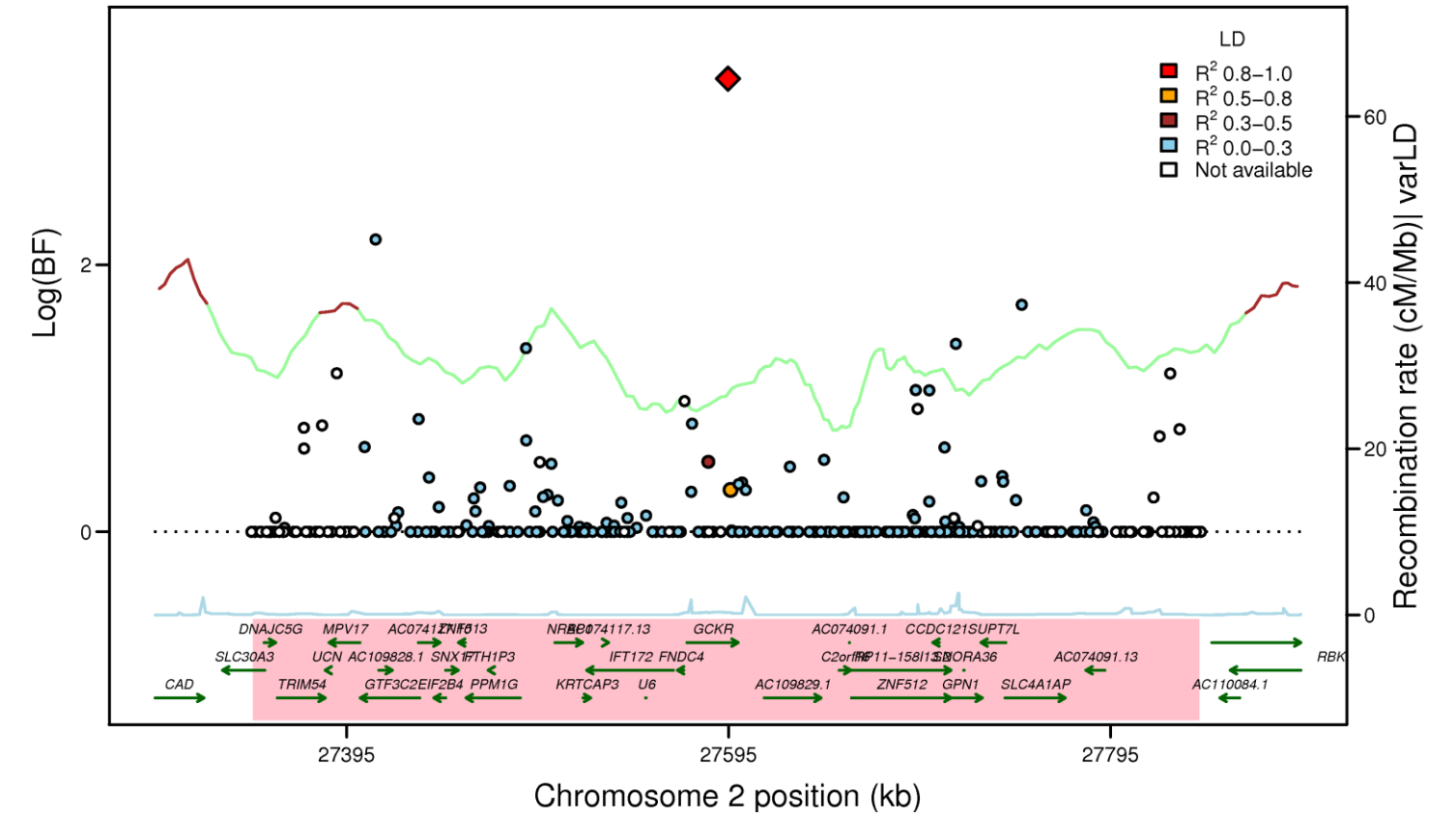


Figure S3E

GCKR: rs780094 (FG EA_MANTRA, LD: HapMap2 CEU)



GCKR: rs780094 (FG AA_MANTRA, LD: HapMap2 YRI)



GCKR: rs780094 (FG TE_MANTRA, LD: HapMap2 YRI)

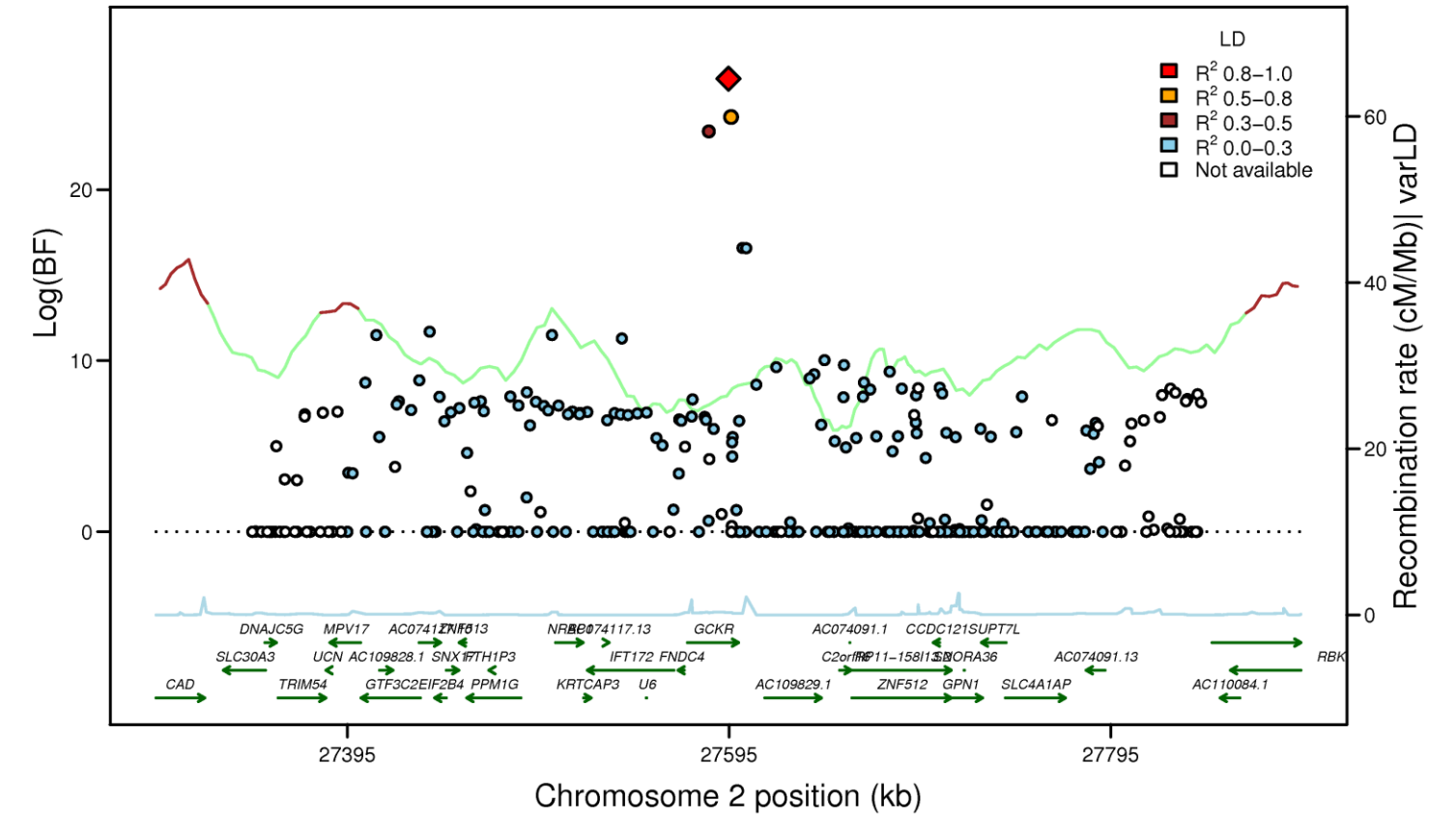
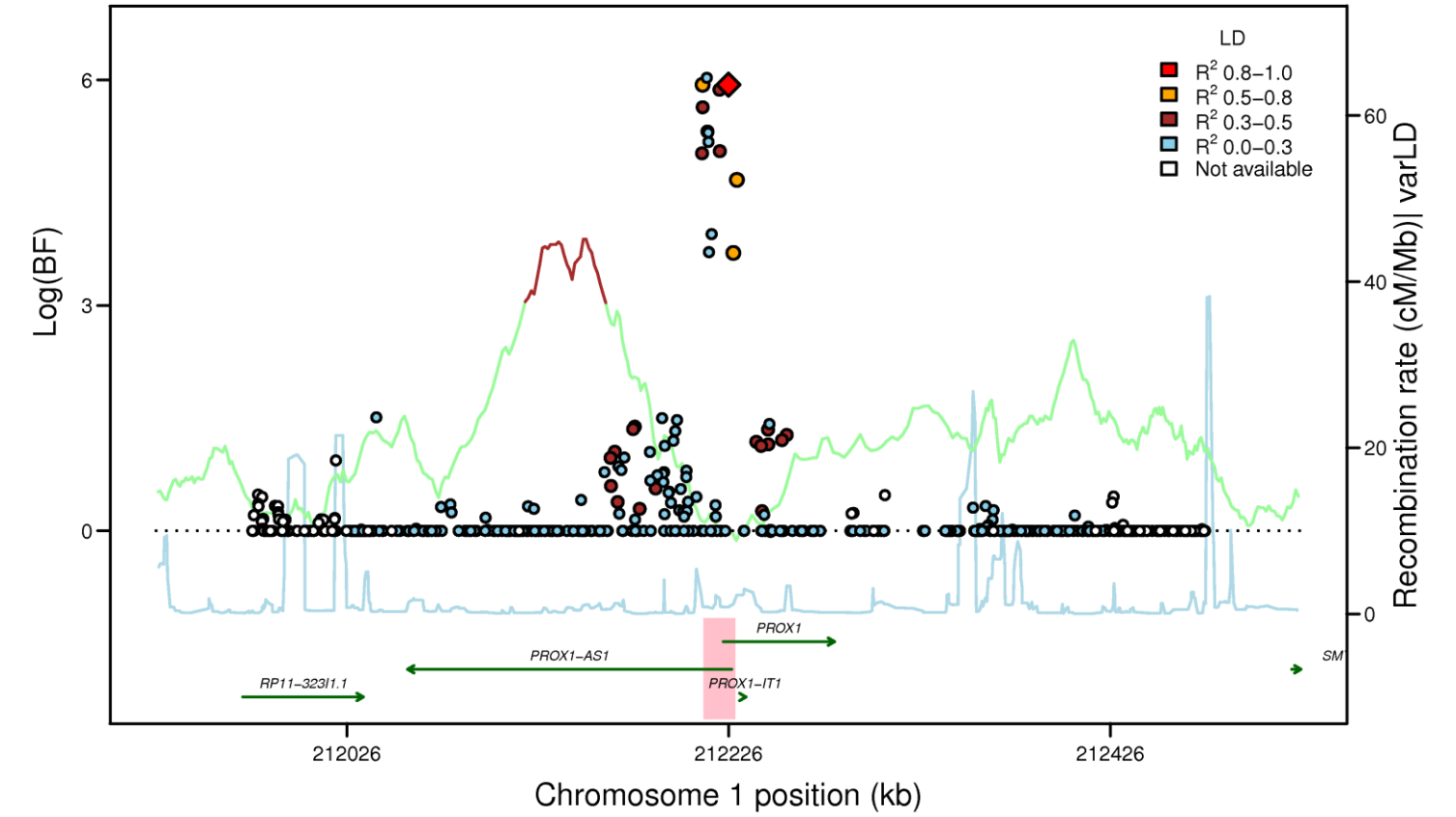
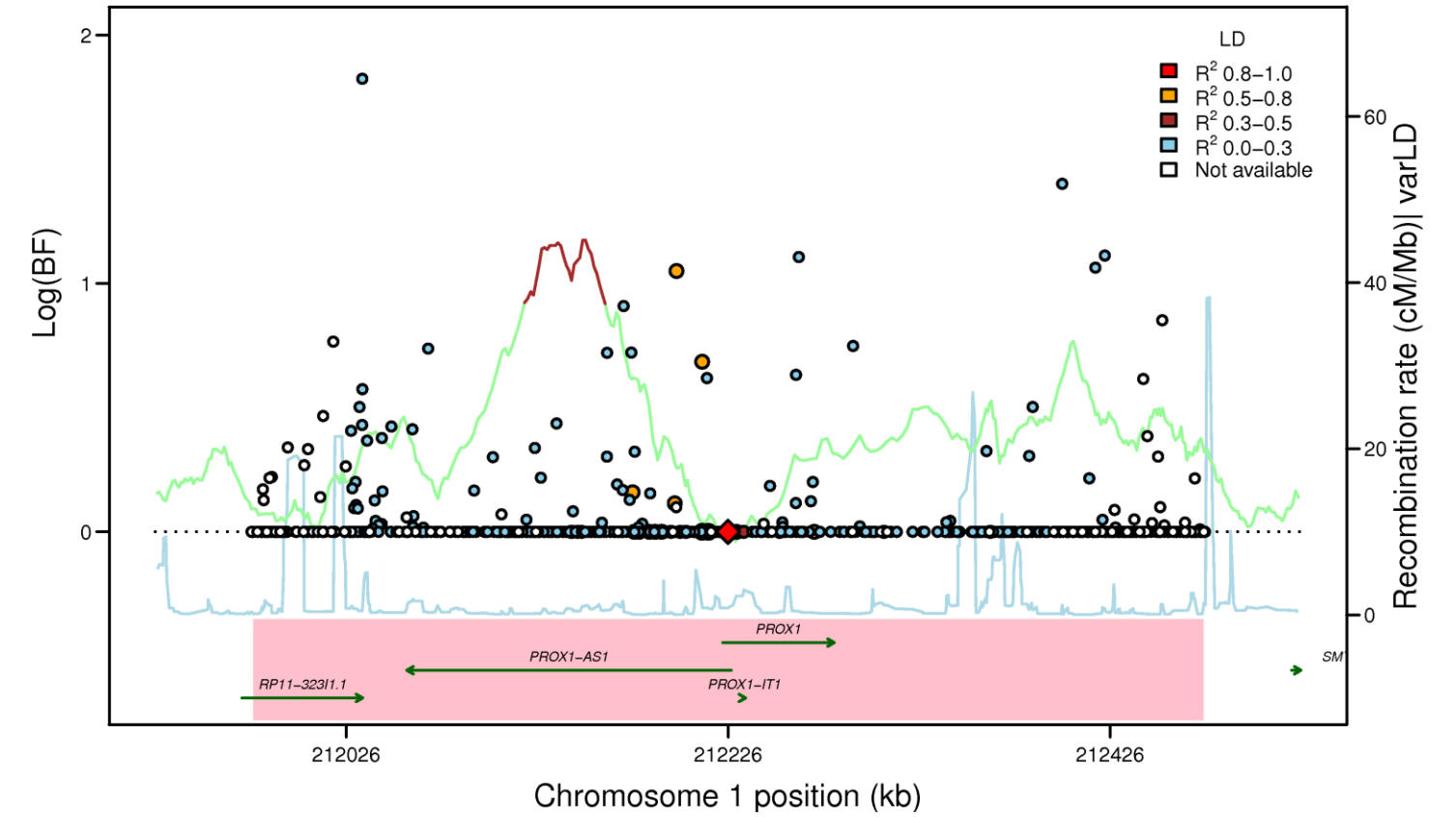


Figure S3F

PROX1: rs340874 (FG EA_MANTRA, LD: HapMap2 CEU)



PROX1: rs340874 (FG AA_MANTRA, LD: HapMap2 YRI)



PROX1: rs340874 (FG TE_MANTRA, LD: HapMap2 YRI)

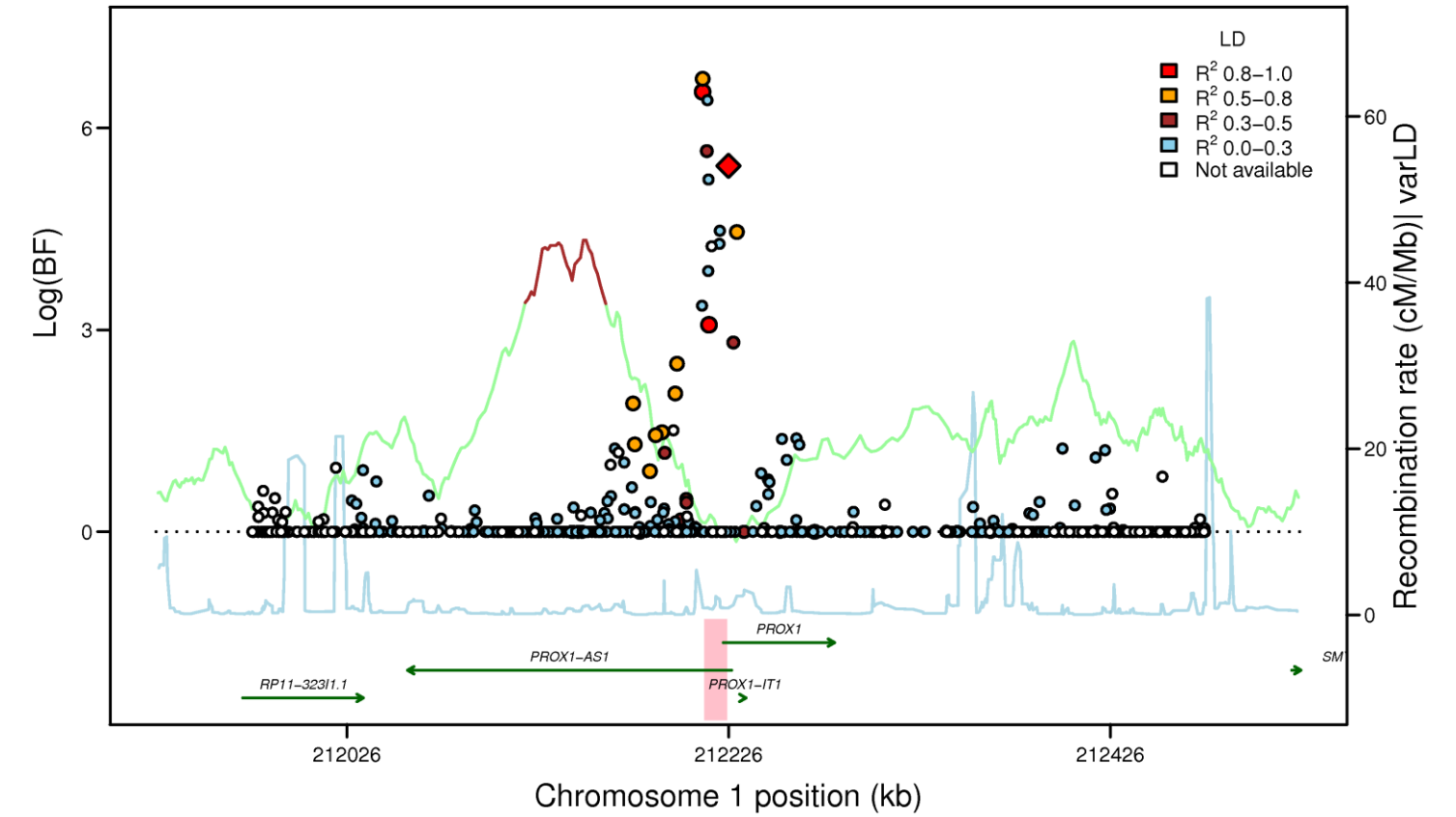
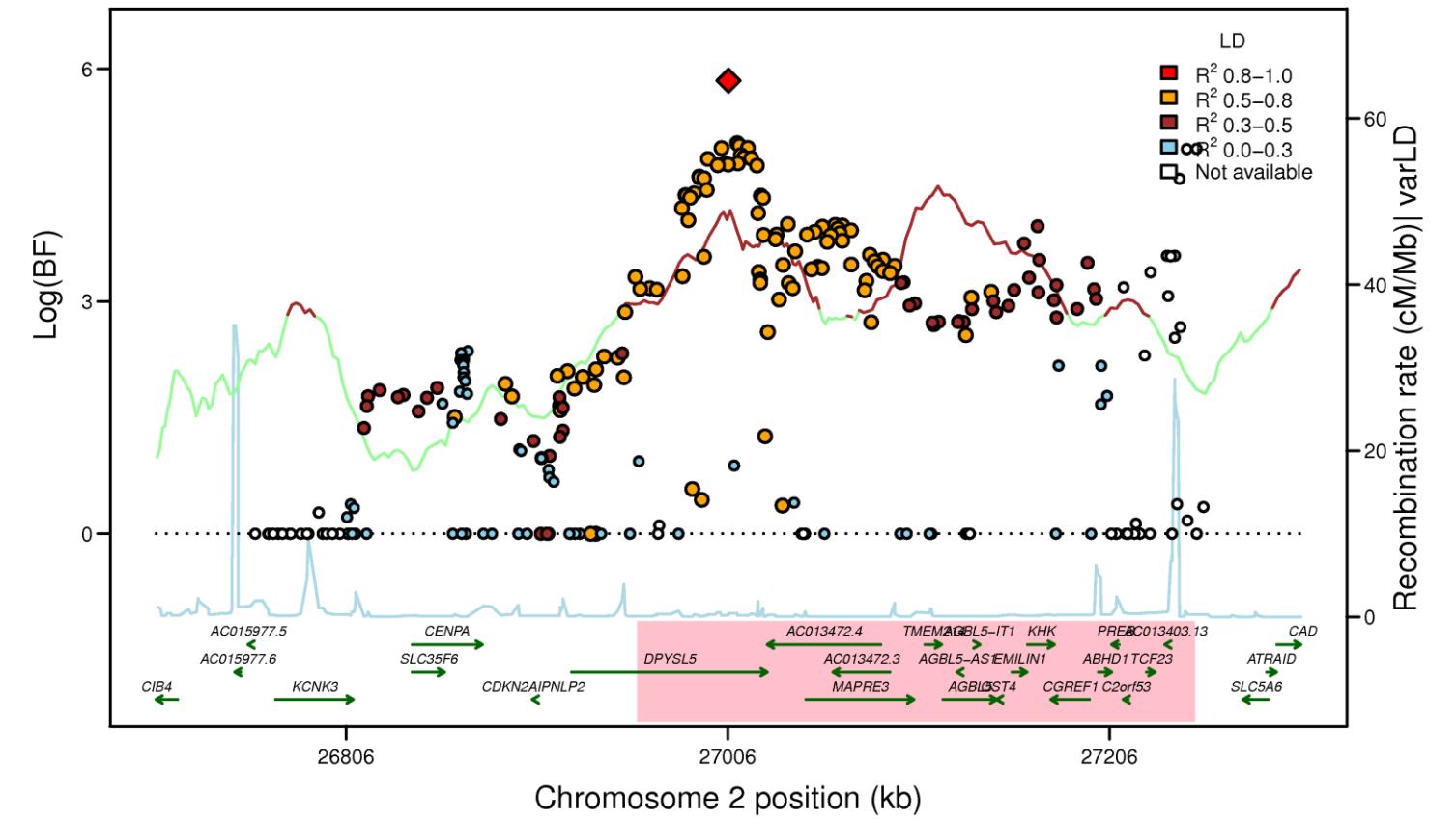
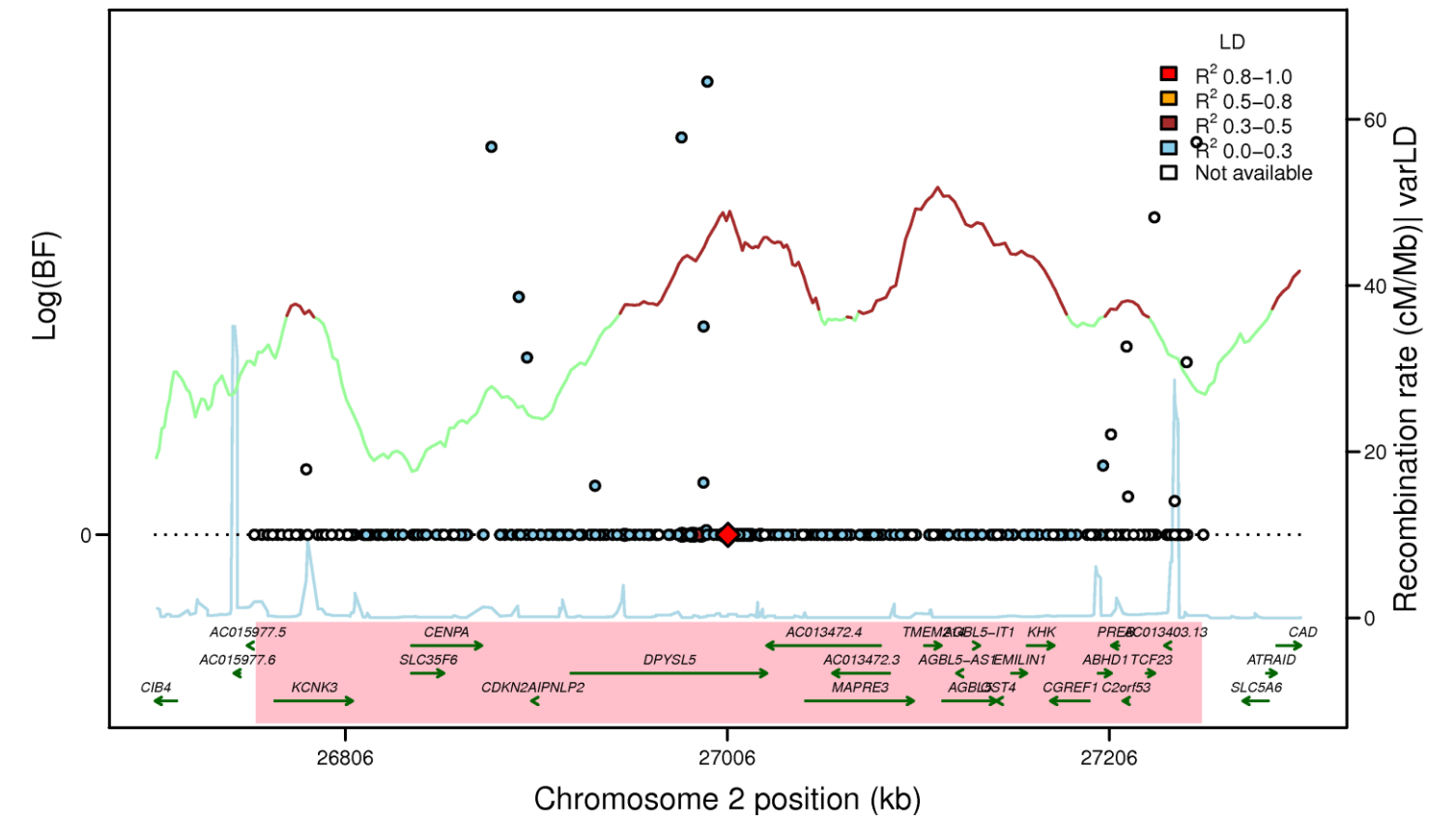


Figure S3G

DPYSL5: rs1371614 (FG EA_MANTRA, LD: HapMap2 CEU)



DPYSL5: rs1371614 (FG AA_MANTRA, LD: HapMap2 YRI)



DPYSL5: rs1371614 (FG TE_MANTRA, LD: HapMap2 YRI)

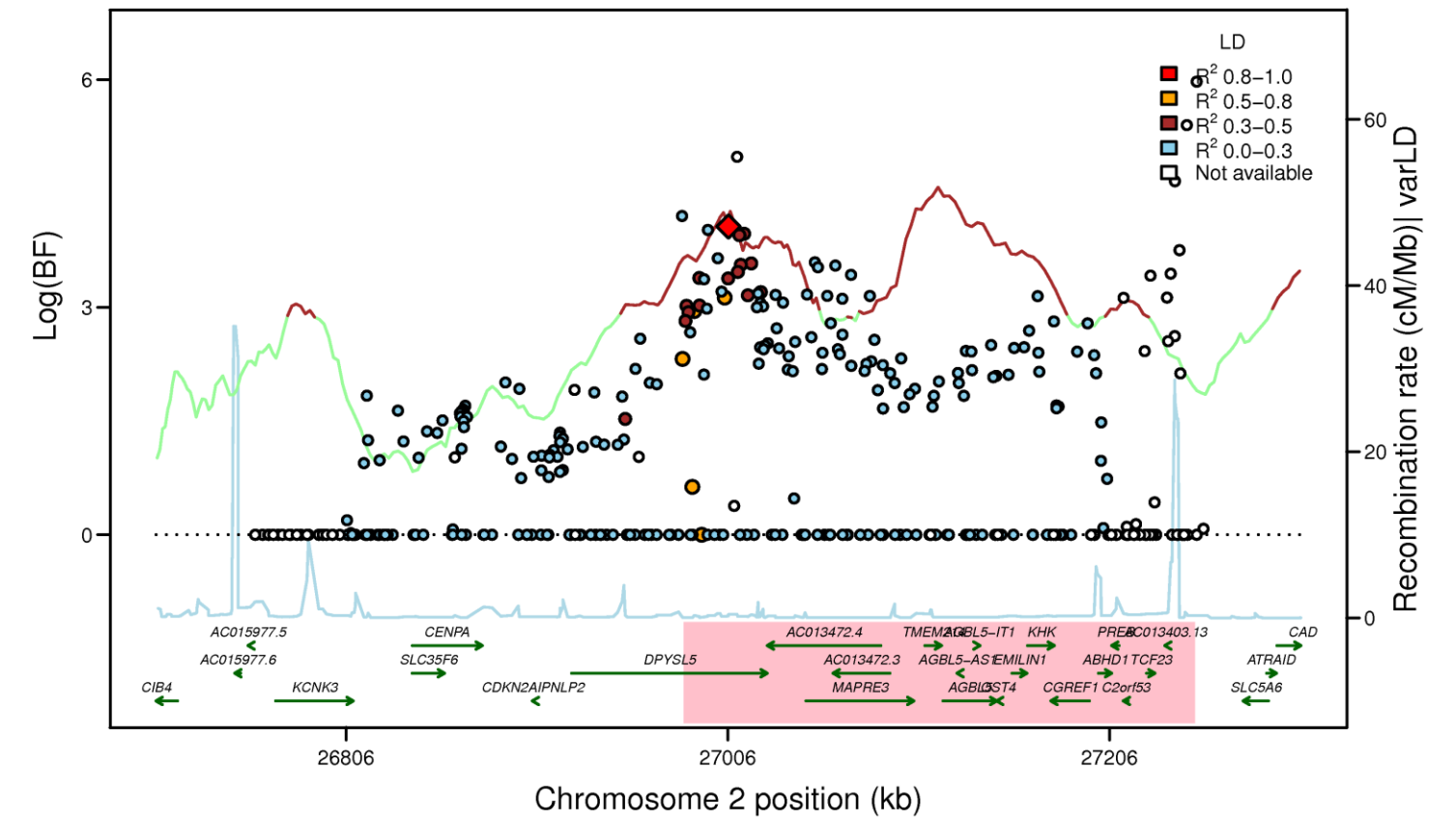
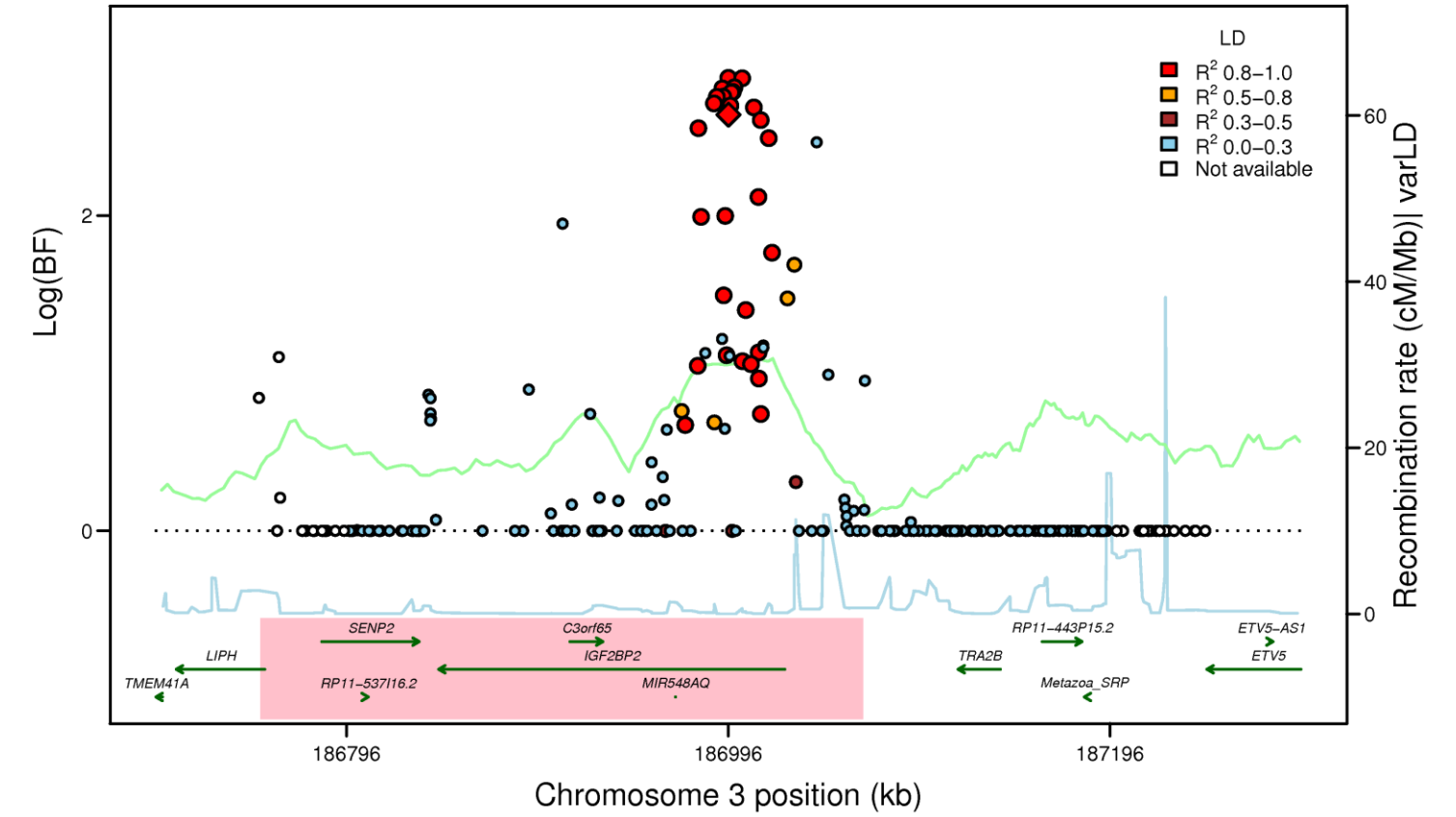
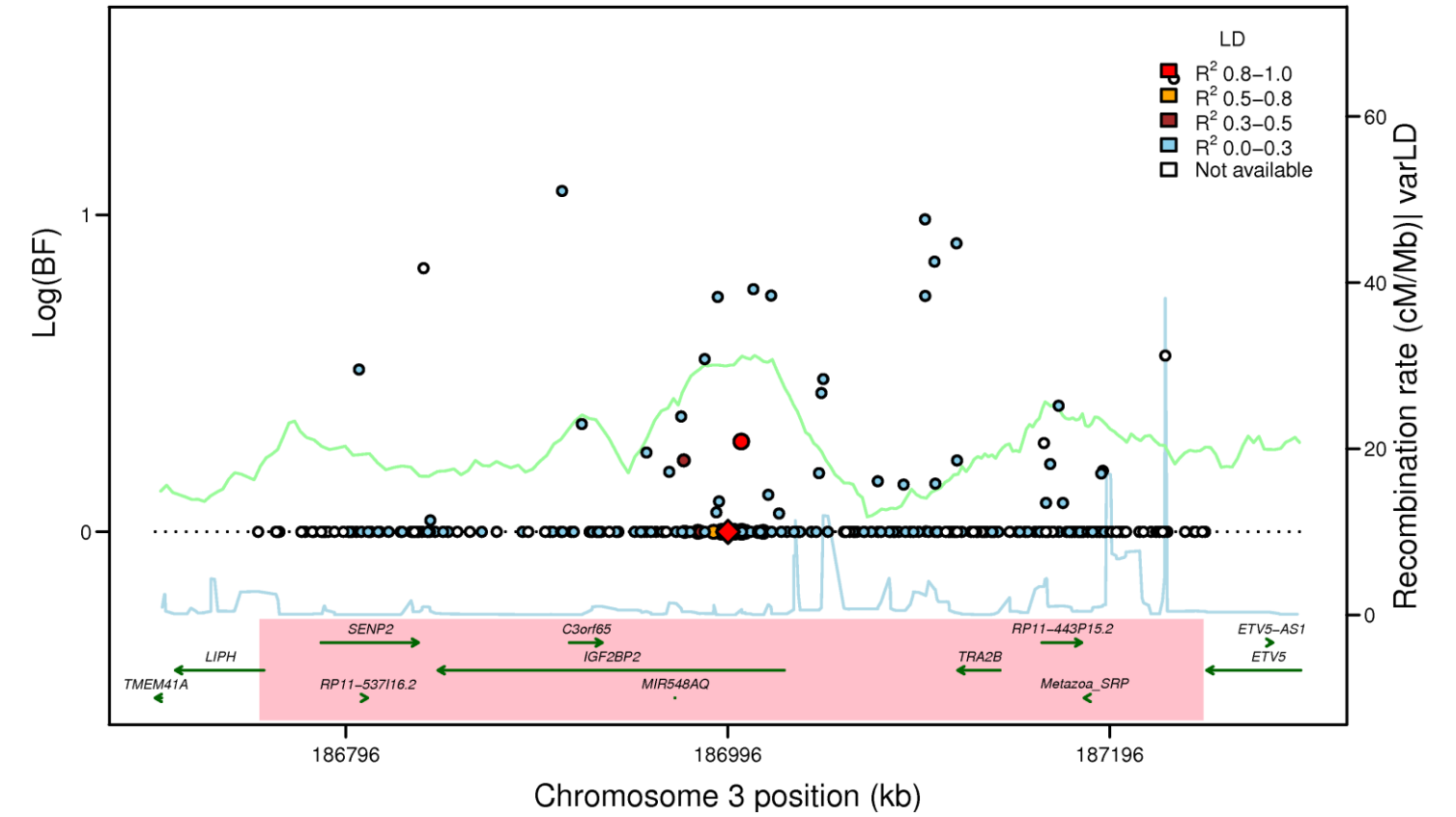


Figure S3H

IGF2BP2: rs7651090 (FG EA_MANTRA, LD: HapMap2 CEU)



IGF2BP2: rs7651090 (FG AA_MANTRA, LD: HapMap2 YRI)



IGF2BP2: rs7651090 (FG TE_MANTRA, LD: HapMap2 YRI)

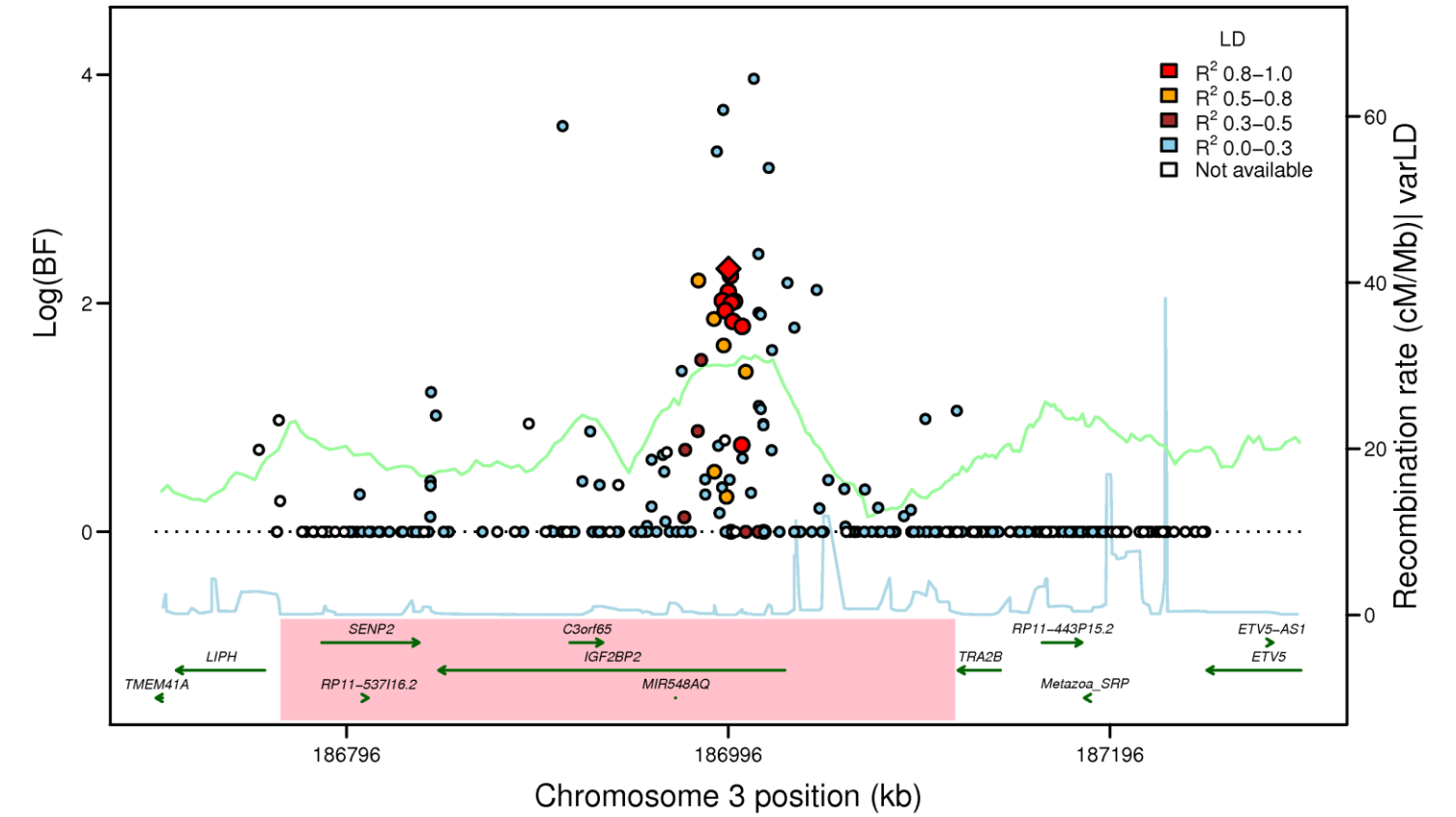
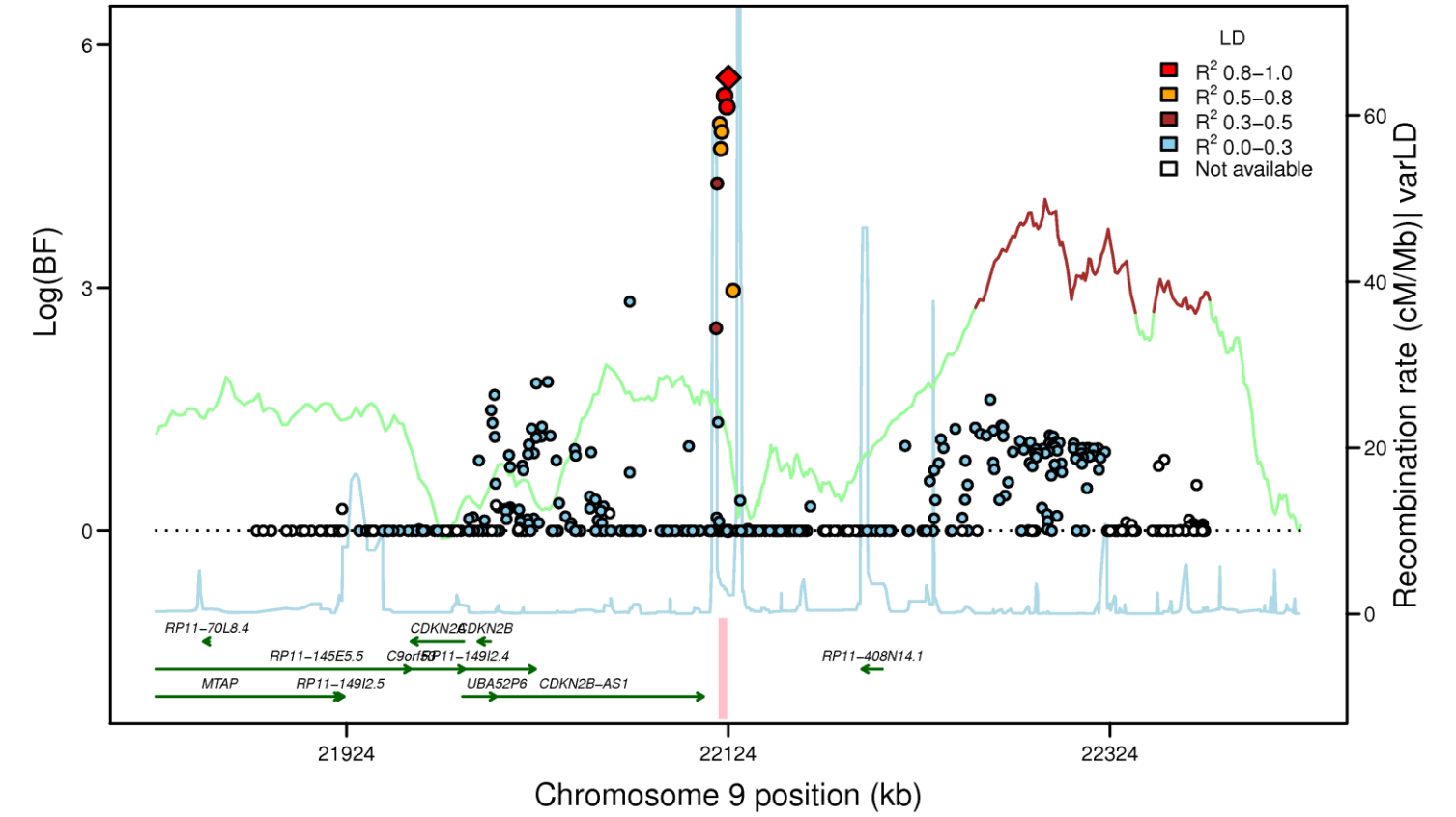
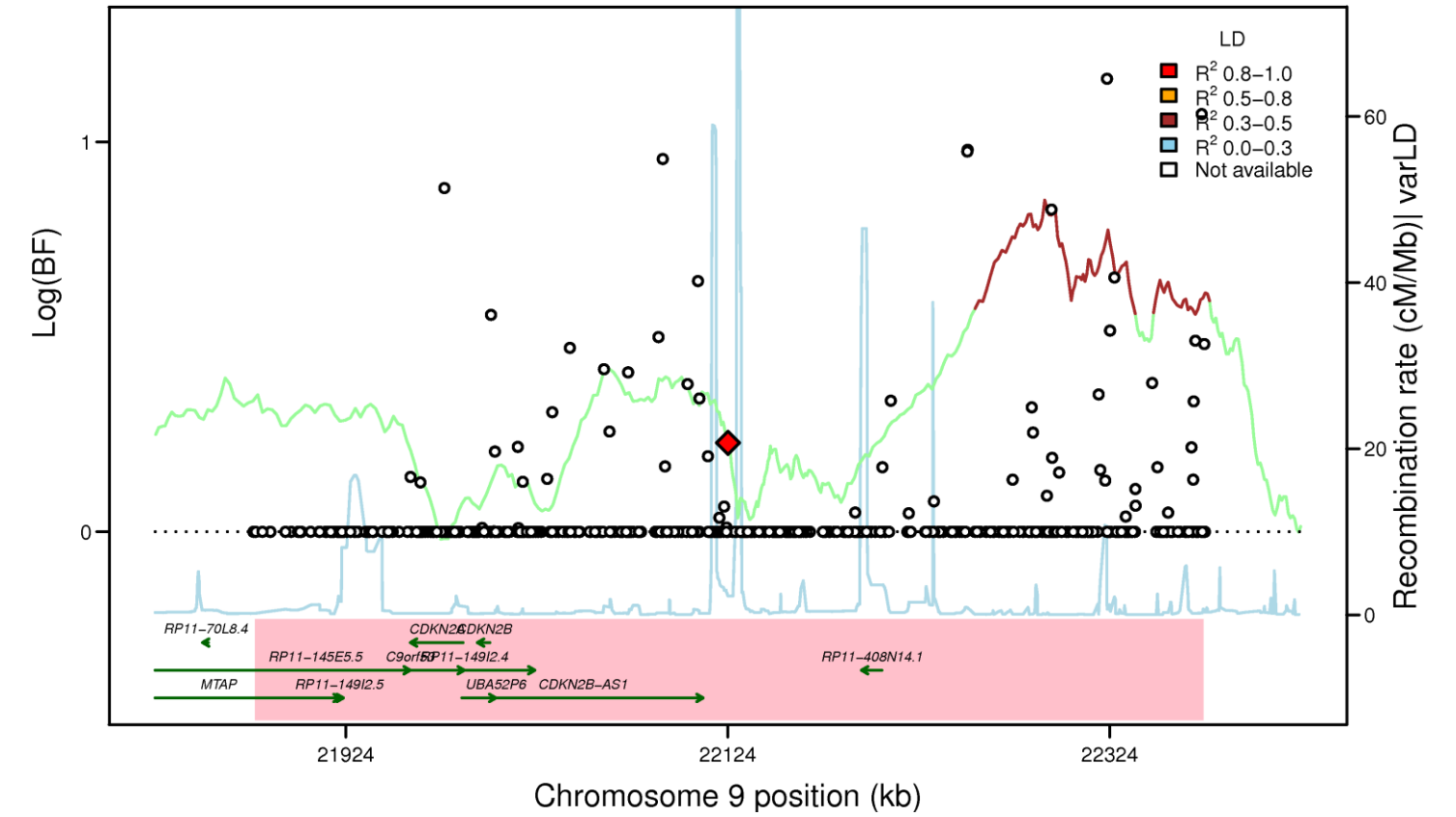


Figure S3I

CDKN2B: rs10811661 (FG EA_MANTRA, LD: HapMap2 CEU)



CDKN2B: rs10811661 (FG AA_MANTRA, LD: HapMap2 YRI)



CDKN2B: rs10811661 (FG TE_MANTRA, LD: HapMap2 YRI)

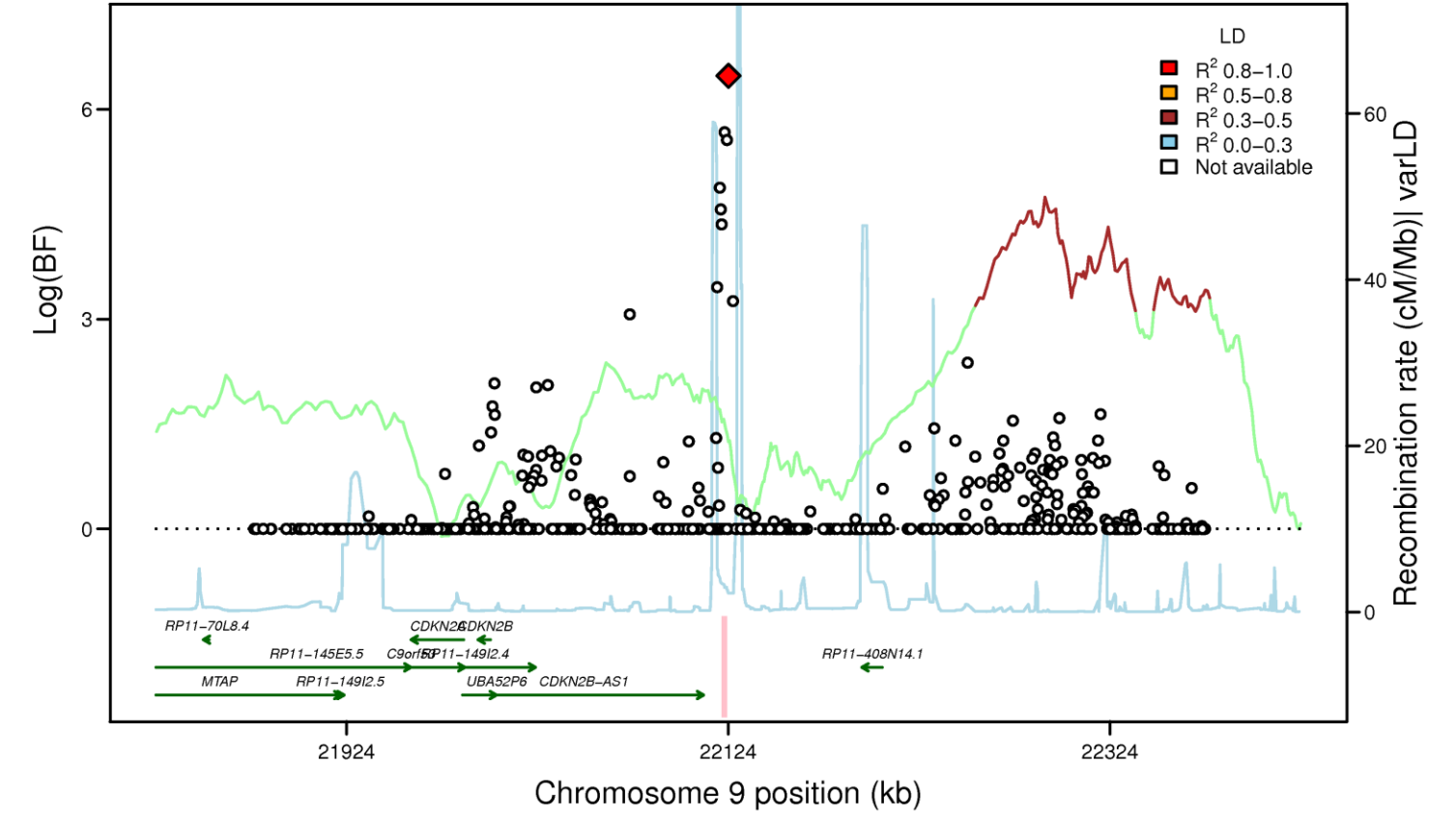
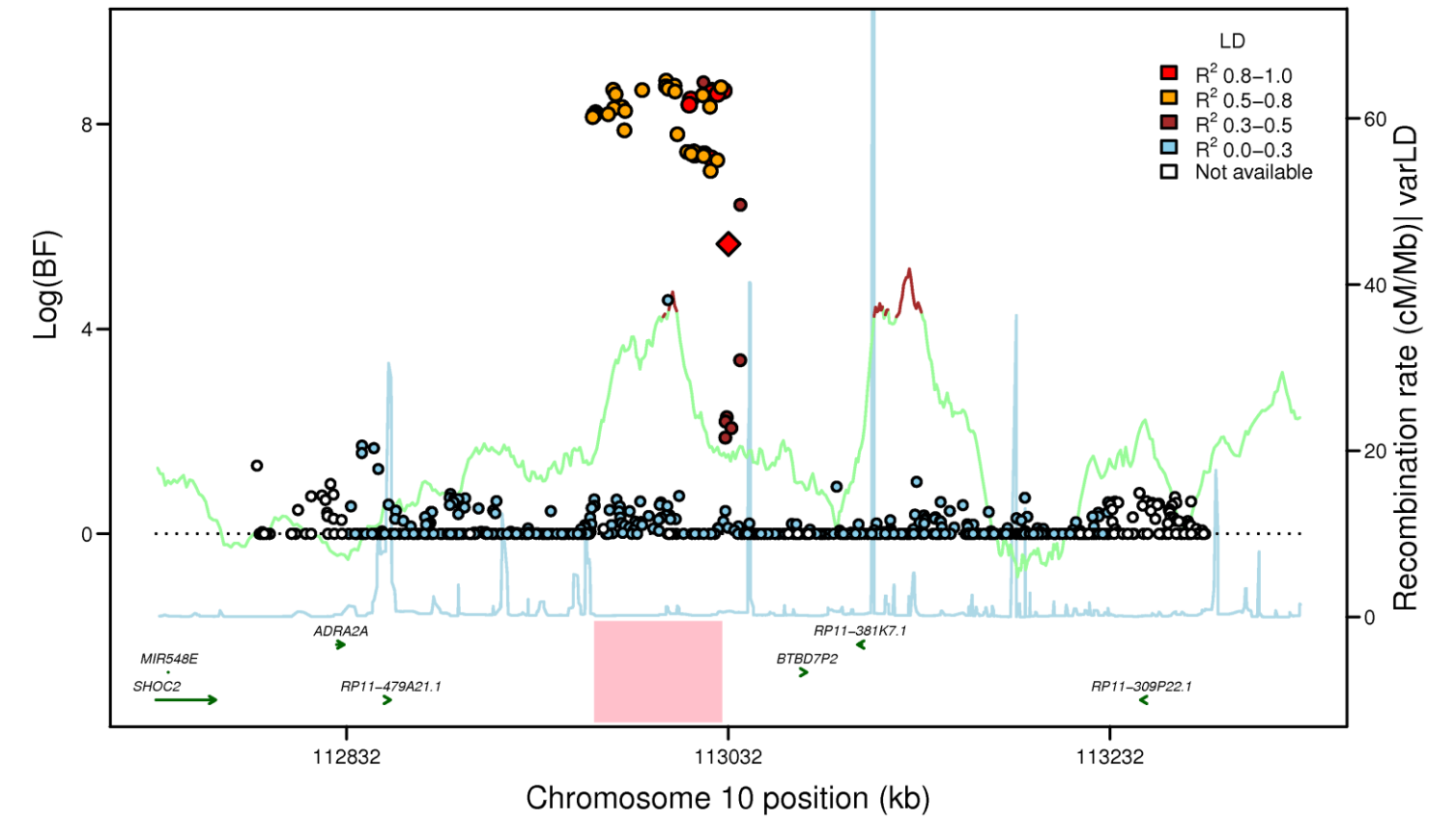
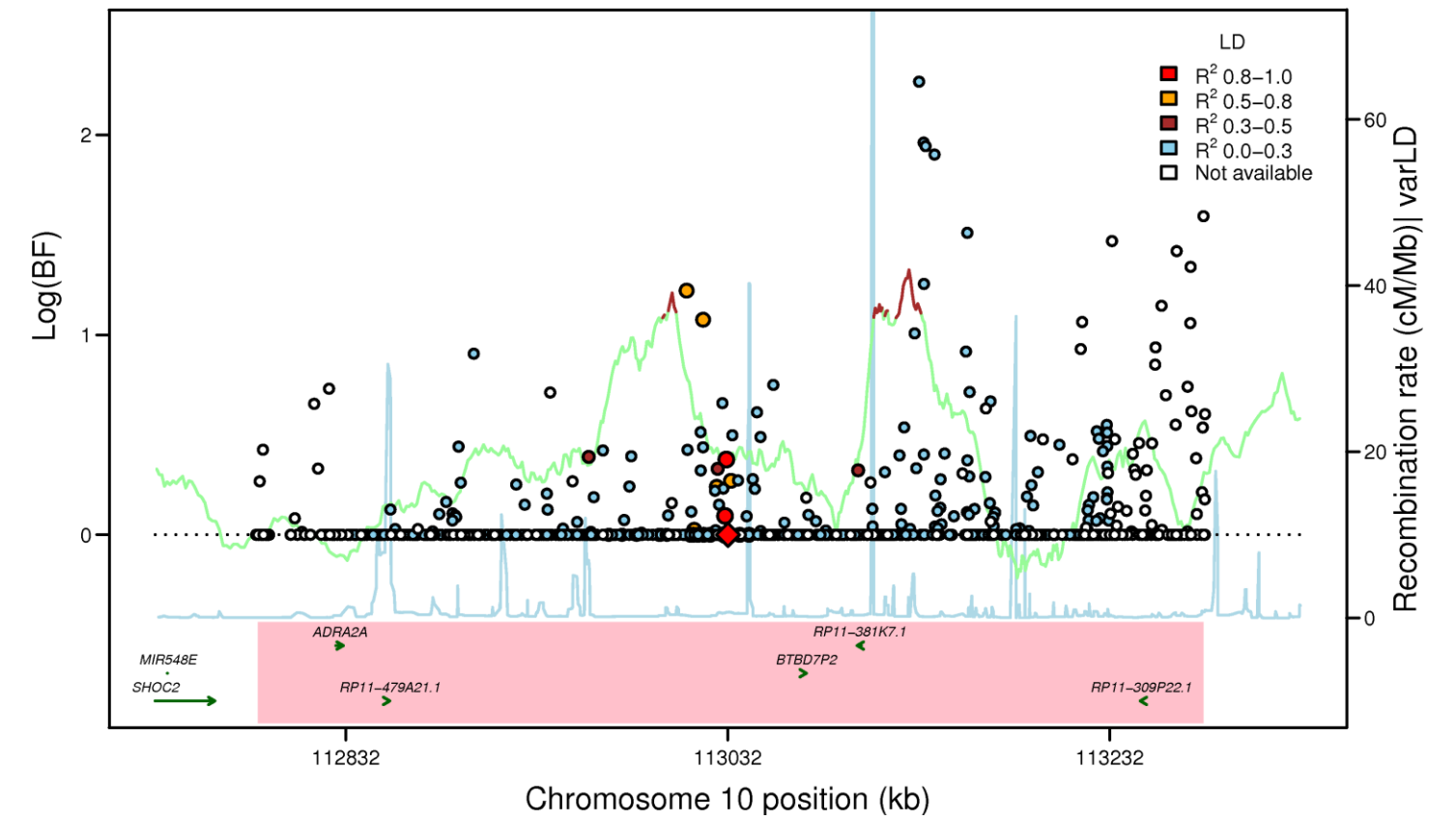


Figure S3J

ADRA2A: rs10885122 (FG EA_MANTRA, LD: HapMap2 CEU)



ADRA2A: rs10885122 (FG AA_MANTRA, LD: HapMap2 YRI)



ADRA2A: rs10885122 (FG TE_MANTRA, LD: HapMap2 YRI)

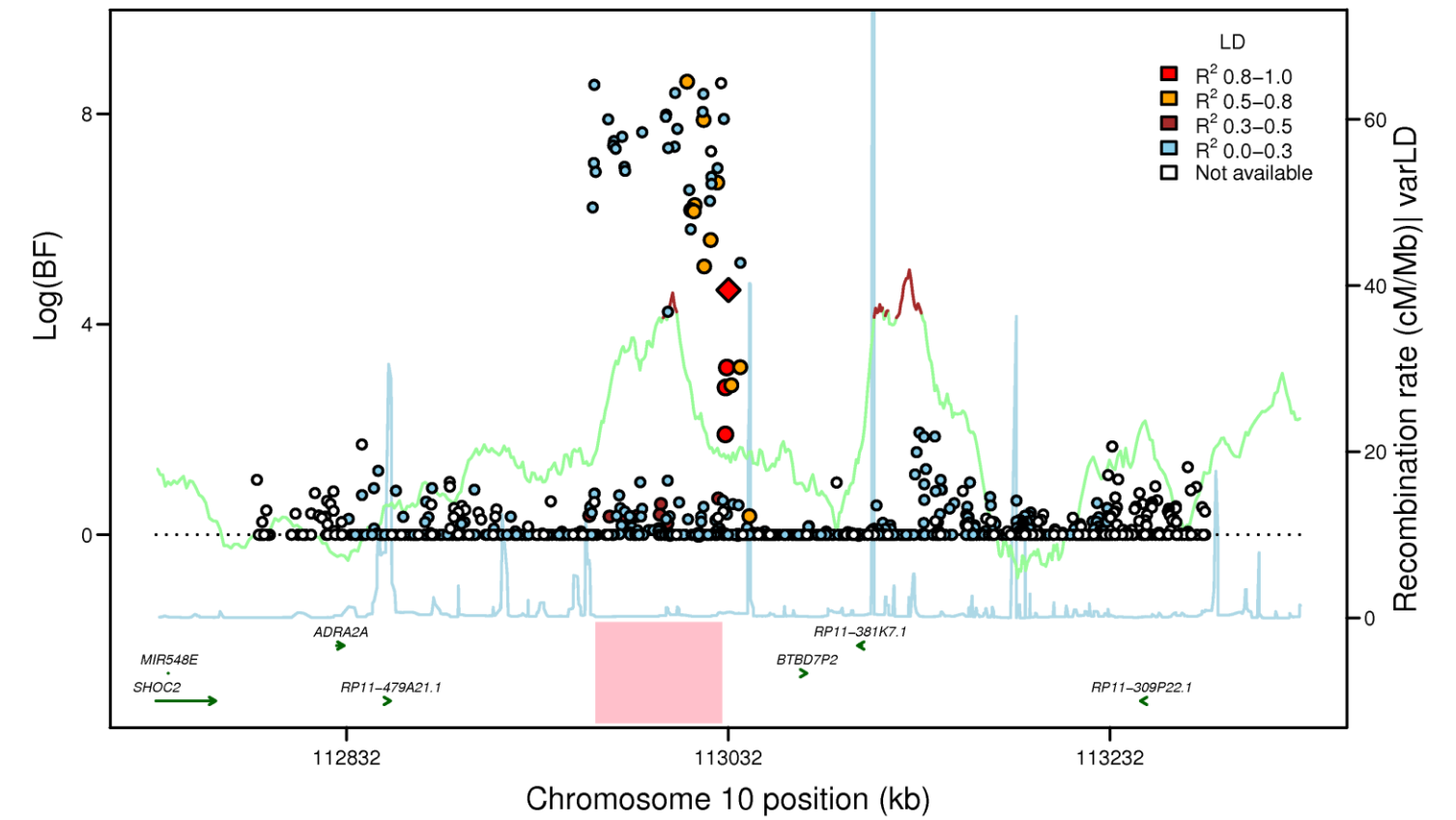
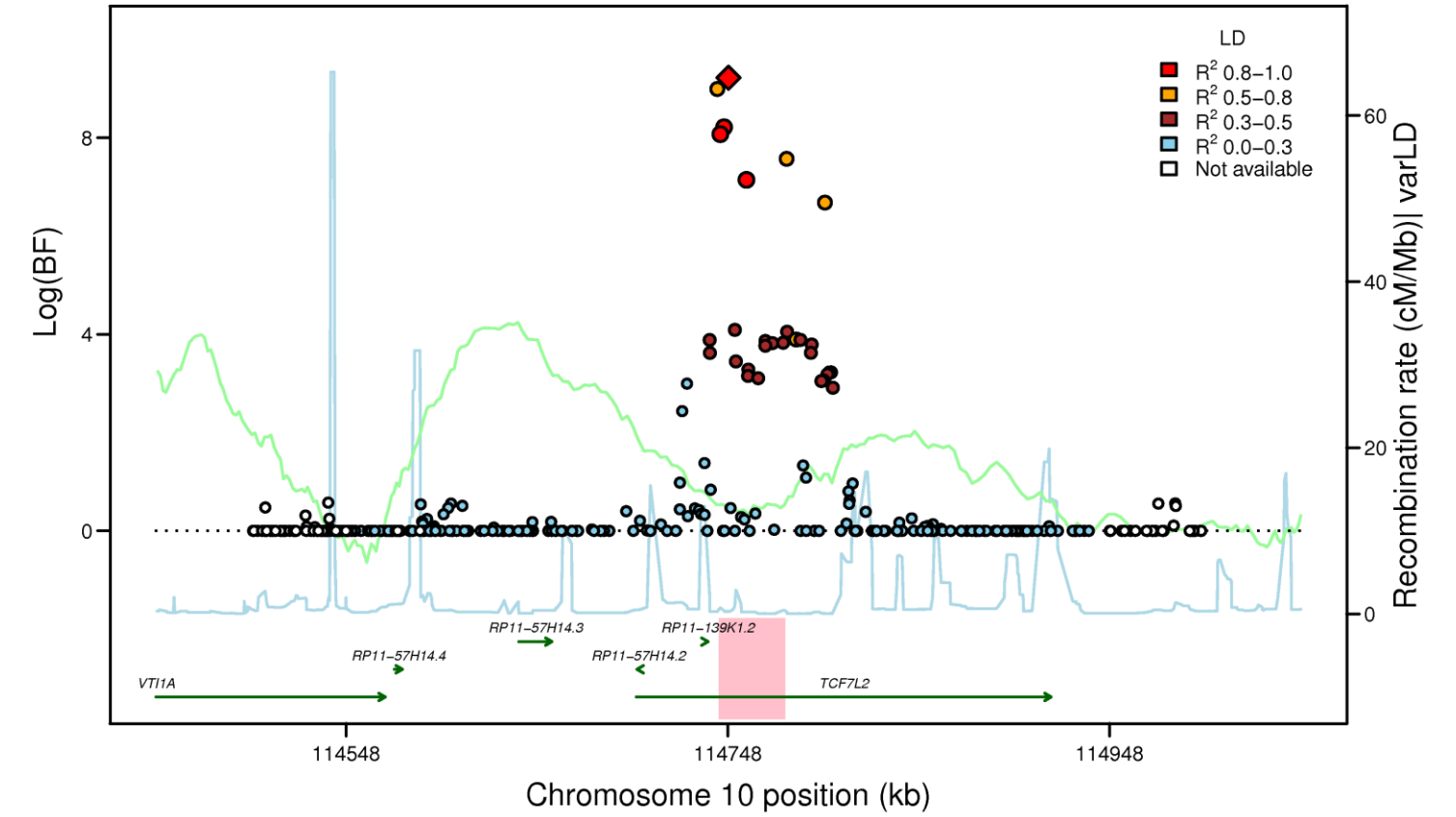
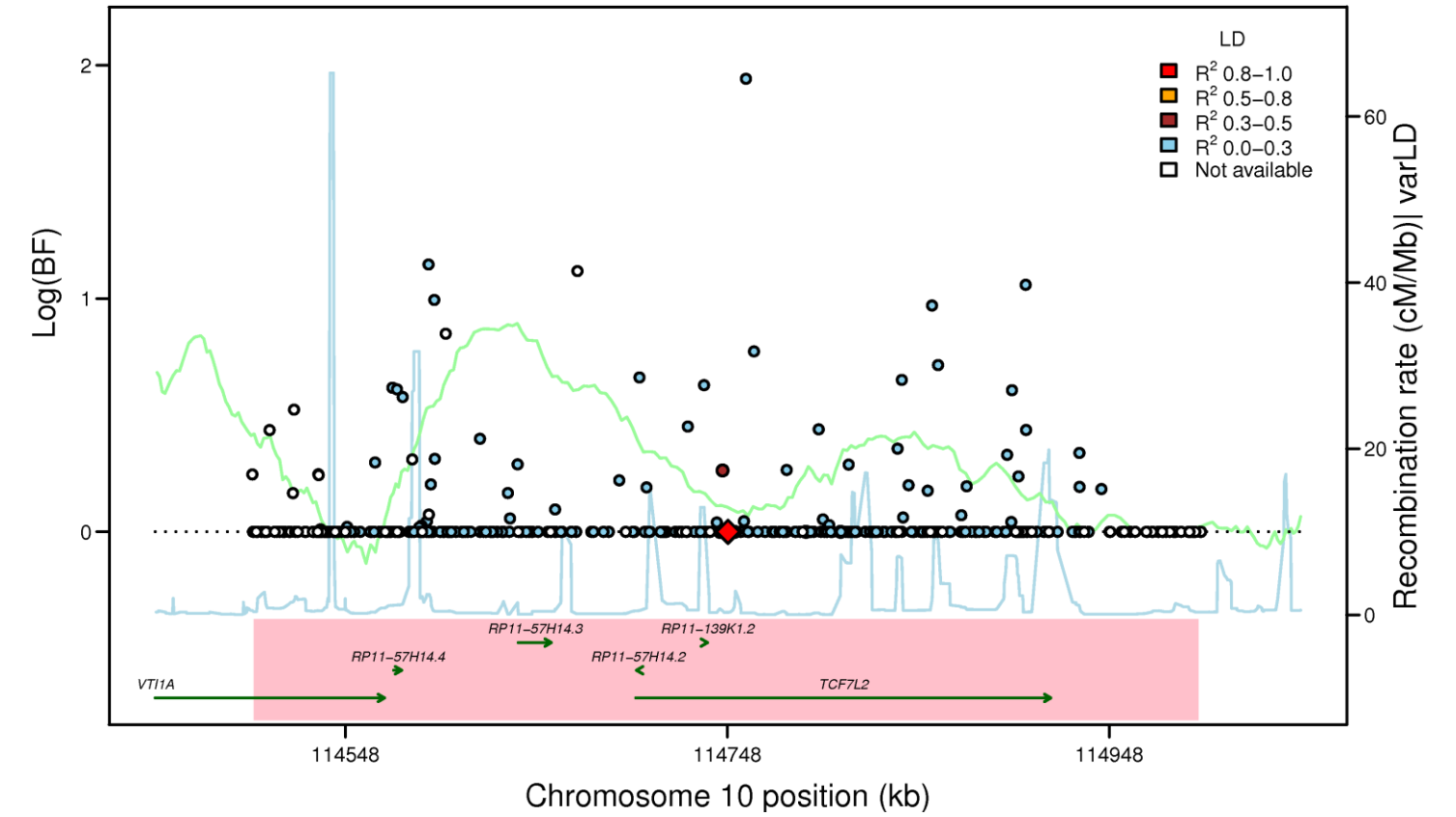


Figure S3K

TCF7L2: rs7903146 (FG EA_MANTRA, LD: HapMap2 CEU)



TCF7L2: rs7903146 (FG AA_MANTRA, LD: HapMap2 YRI)



TCF7L2: rs7903146 (FG TE_MANTRA, LD: HapMap2 YRI)

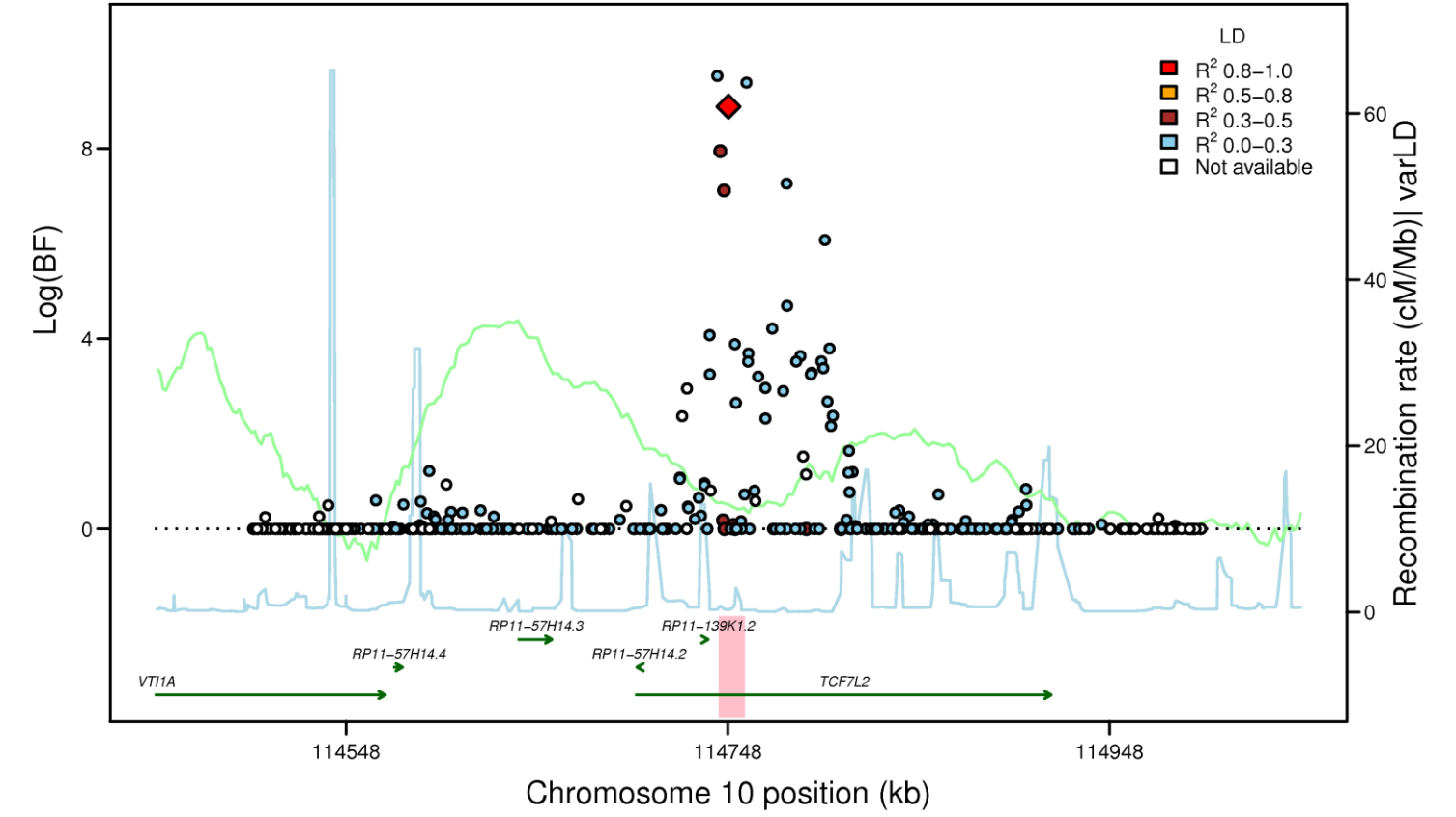
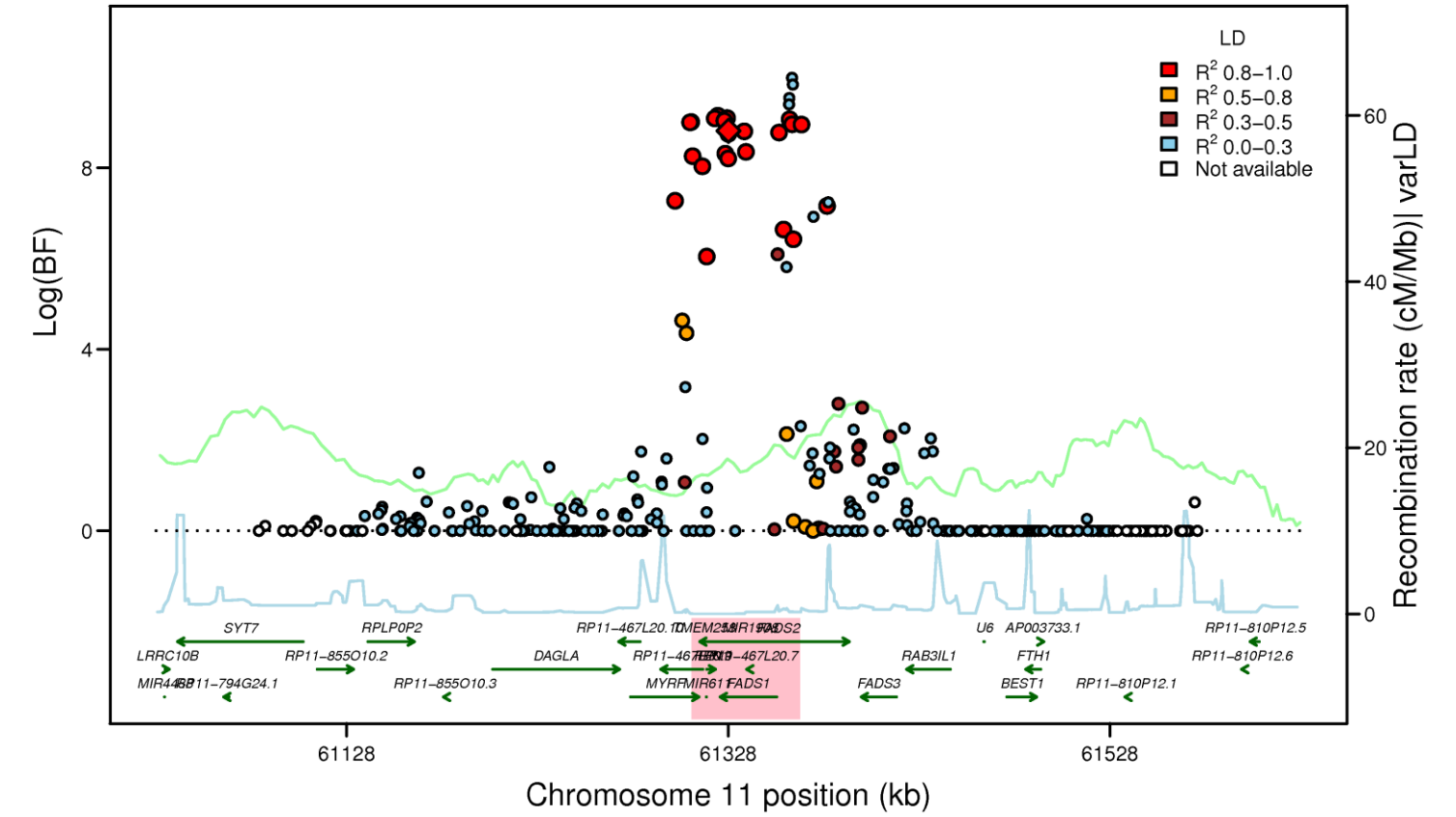
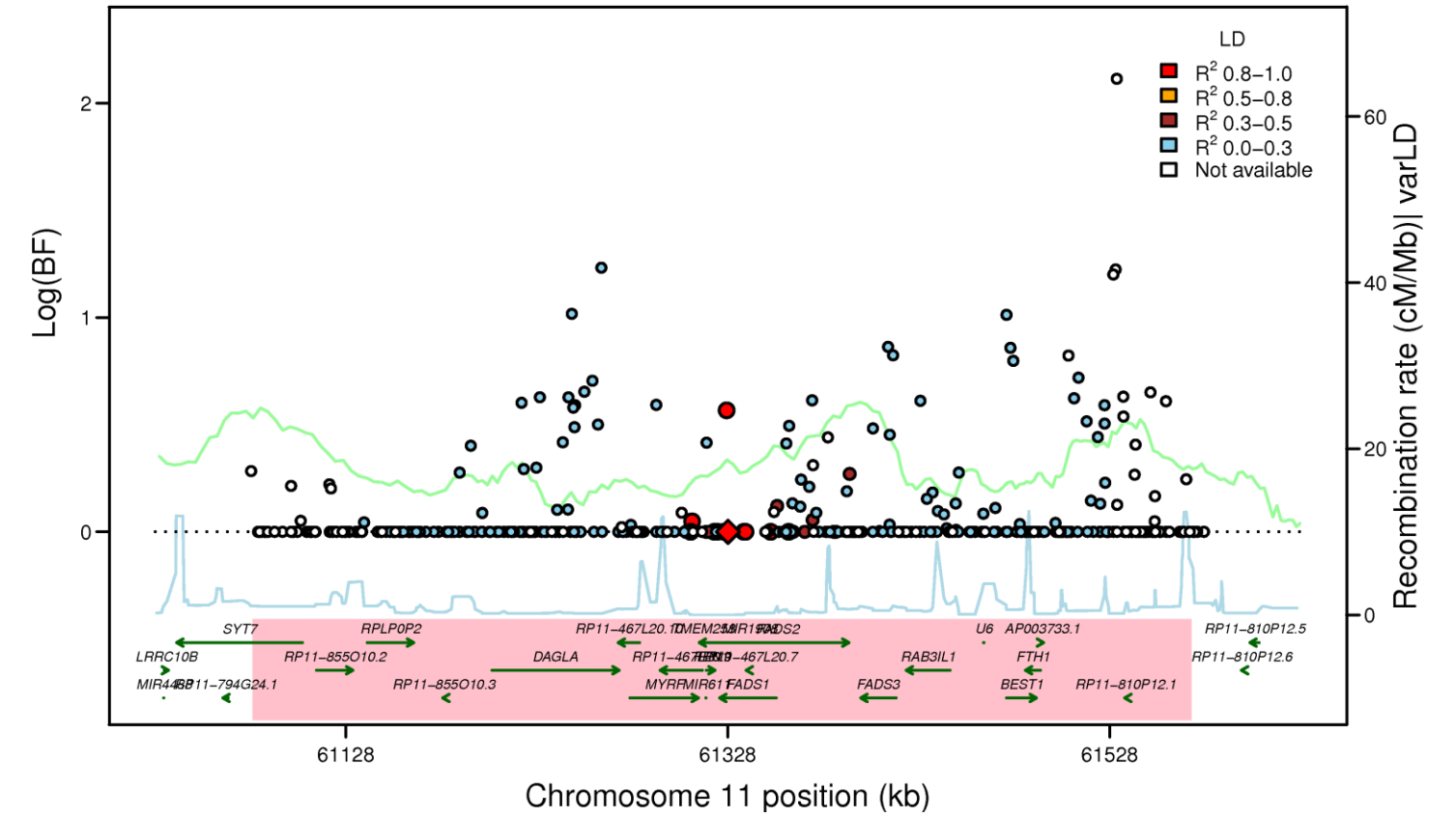


Figure S3L

FADS1: rs174550 (FG EA_MANTRA, LD: HapMap2 CEU)



FADS1: rs174550 (FG AA_MANTRA, LD: HapMap2 YRI)



FADS1: rs174550 (FG TE_MANTRA, LD: HapMap2 YRI)

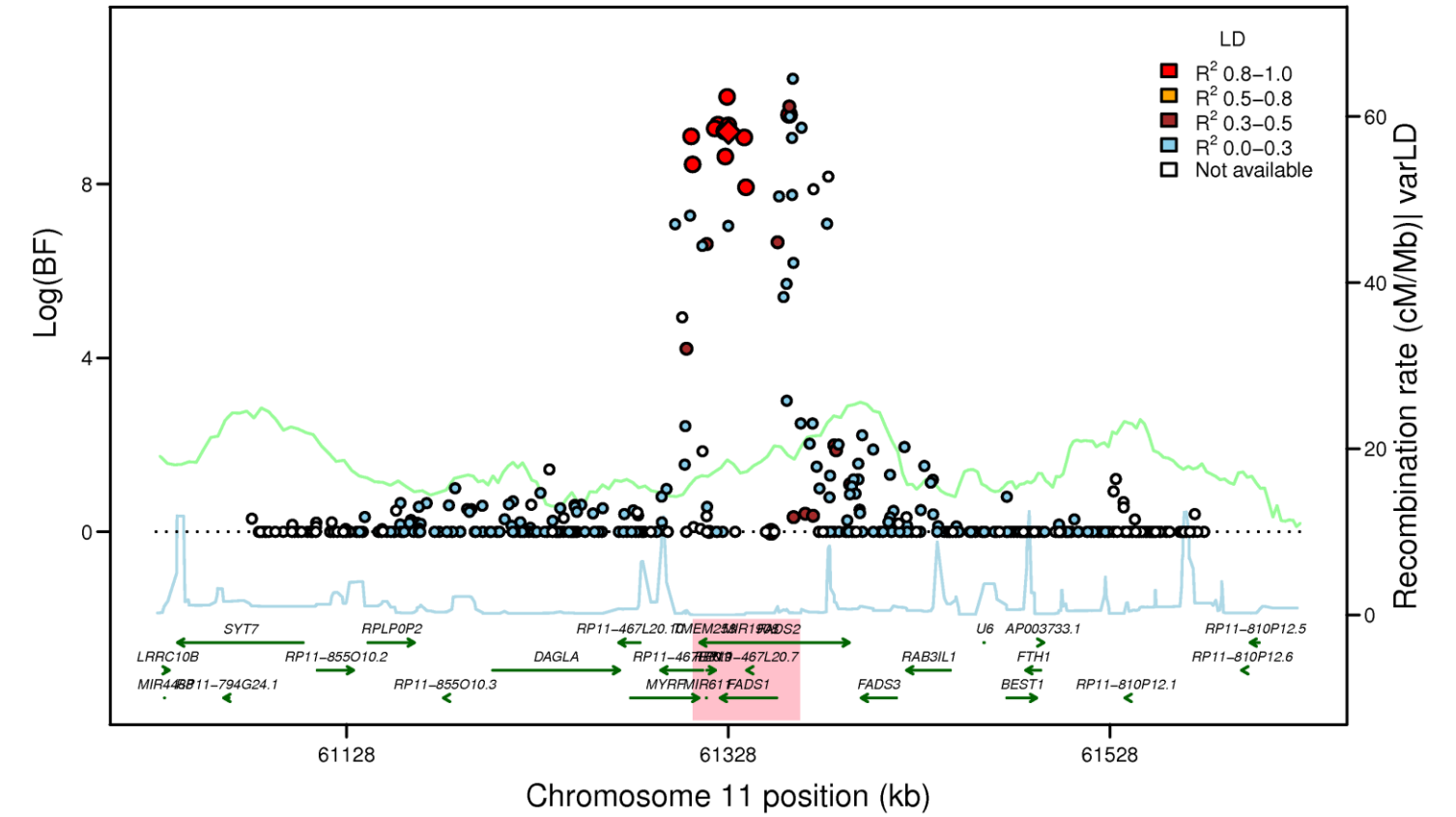
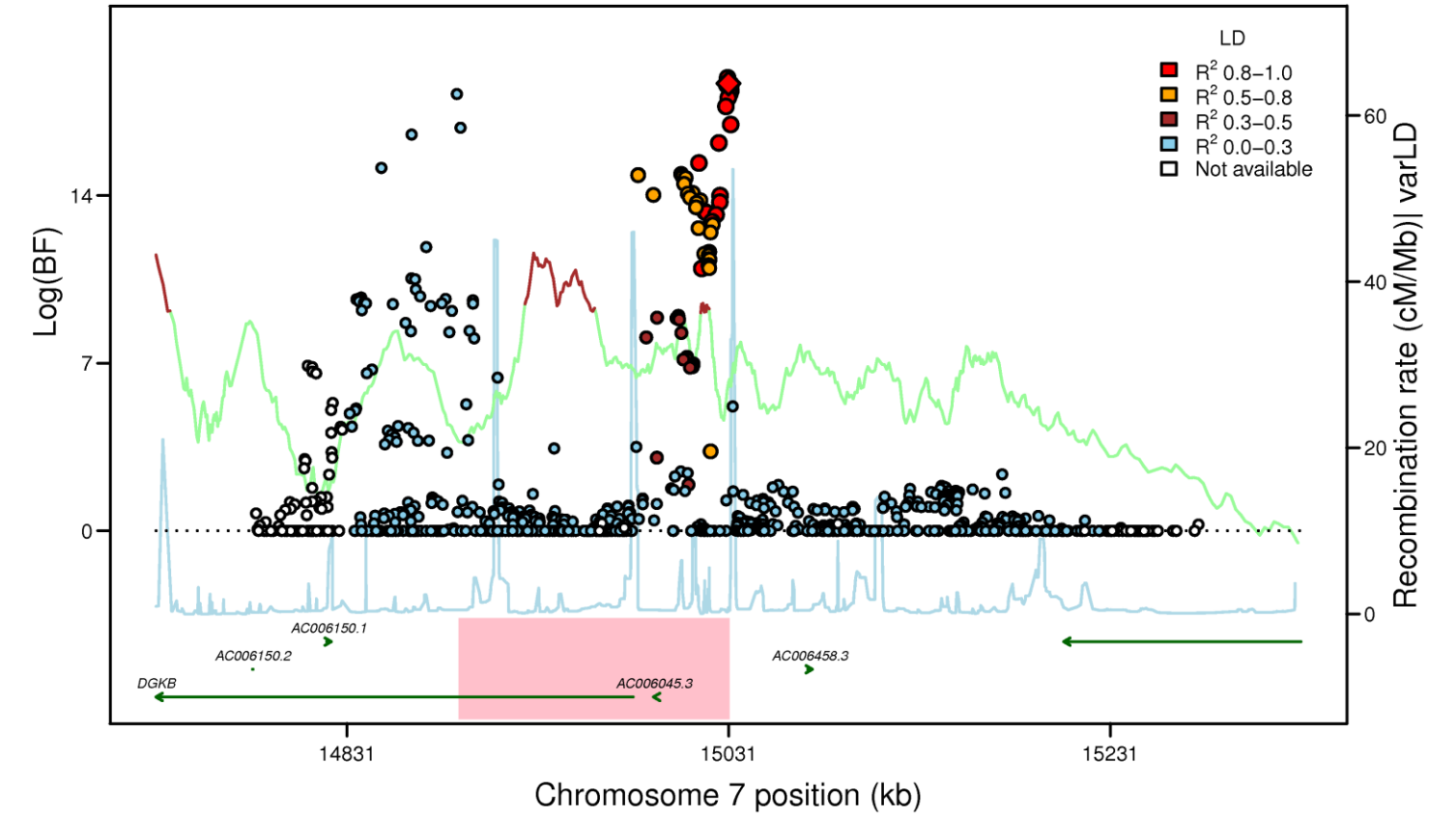
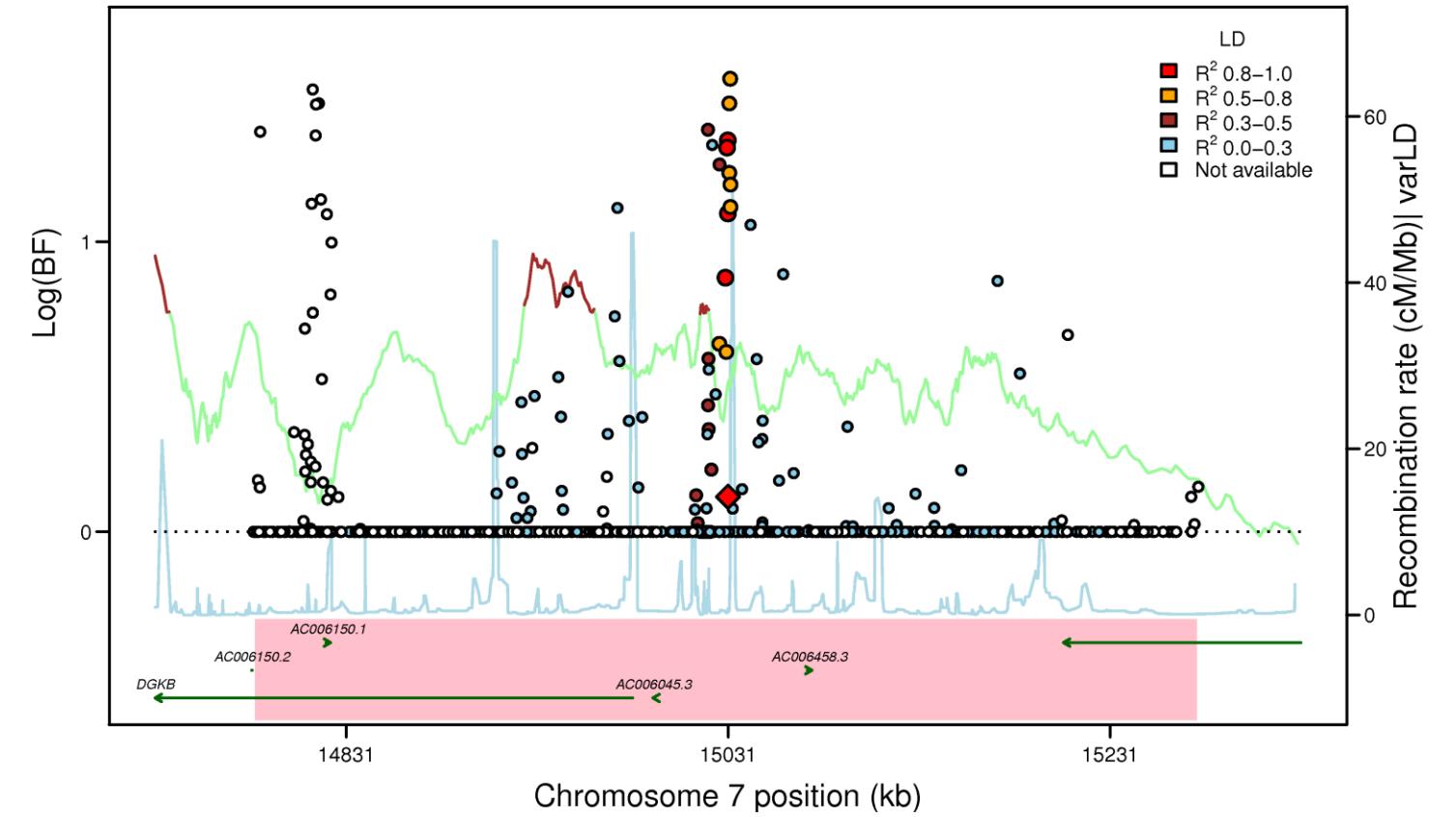


Figure S3M

DGKB–TMEM195: rs2191349 (FG EA_MANTRA, LD: HapMap2 CEU)



DGKB–TMEM195: rs2191349 (FG AA_MANTRA, LD: HapMap2 YRI)



DGKB–TMEM195: rs2191349 (FG TE_MANTRA, LD: HapMap2 YRI)

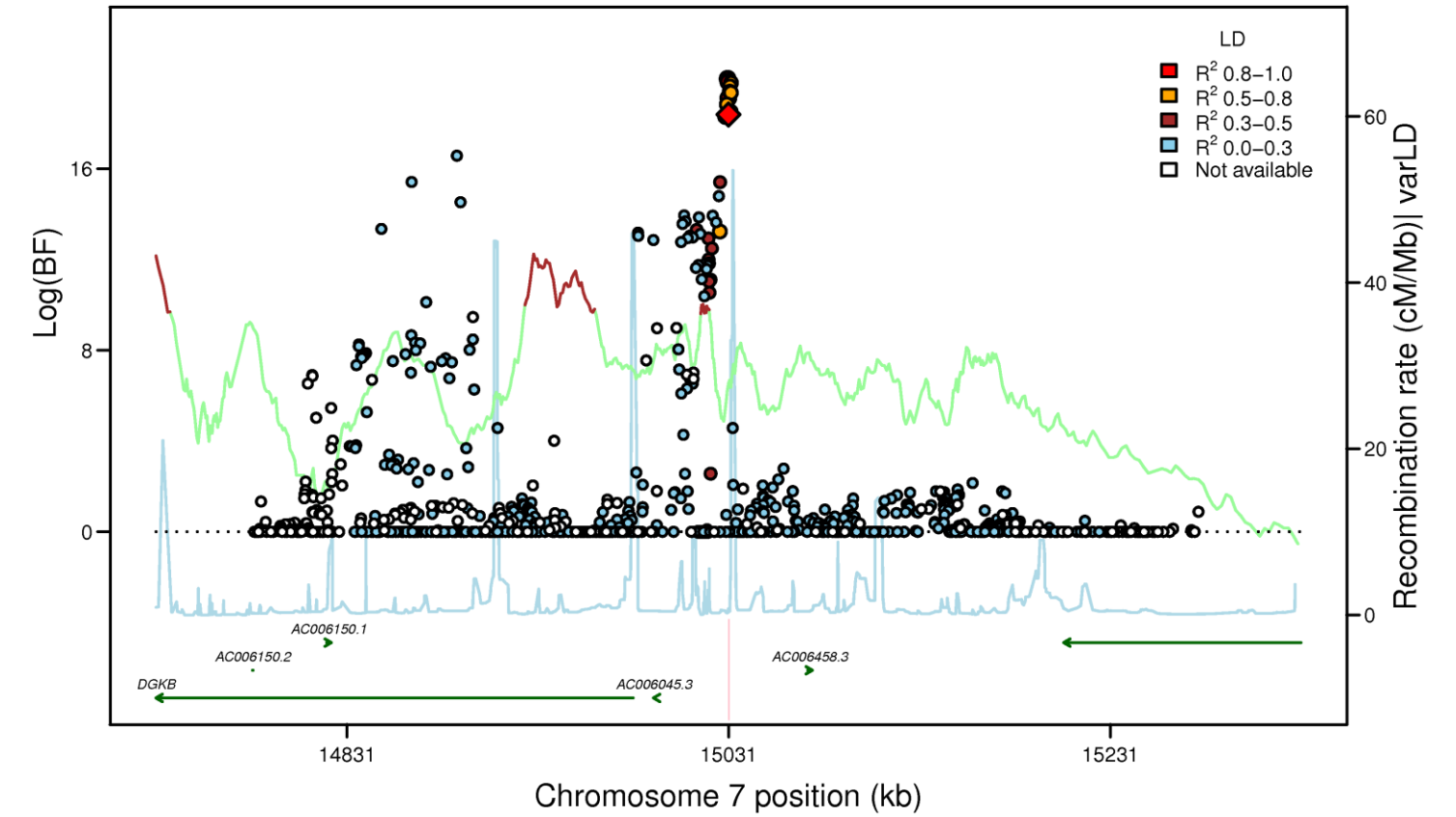
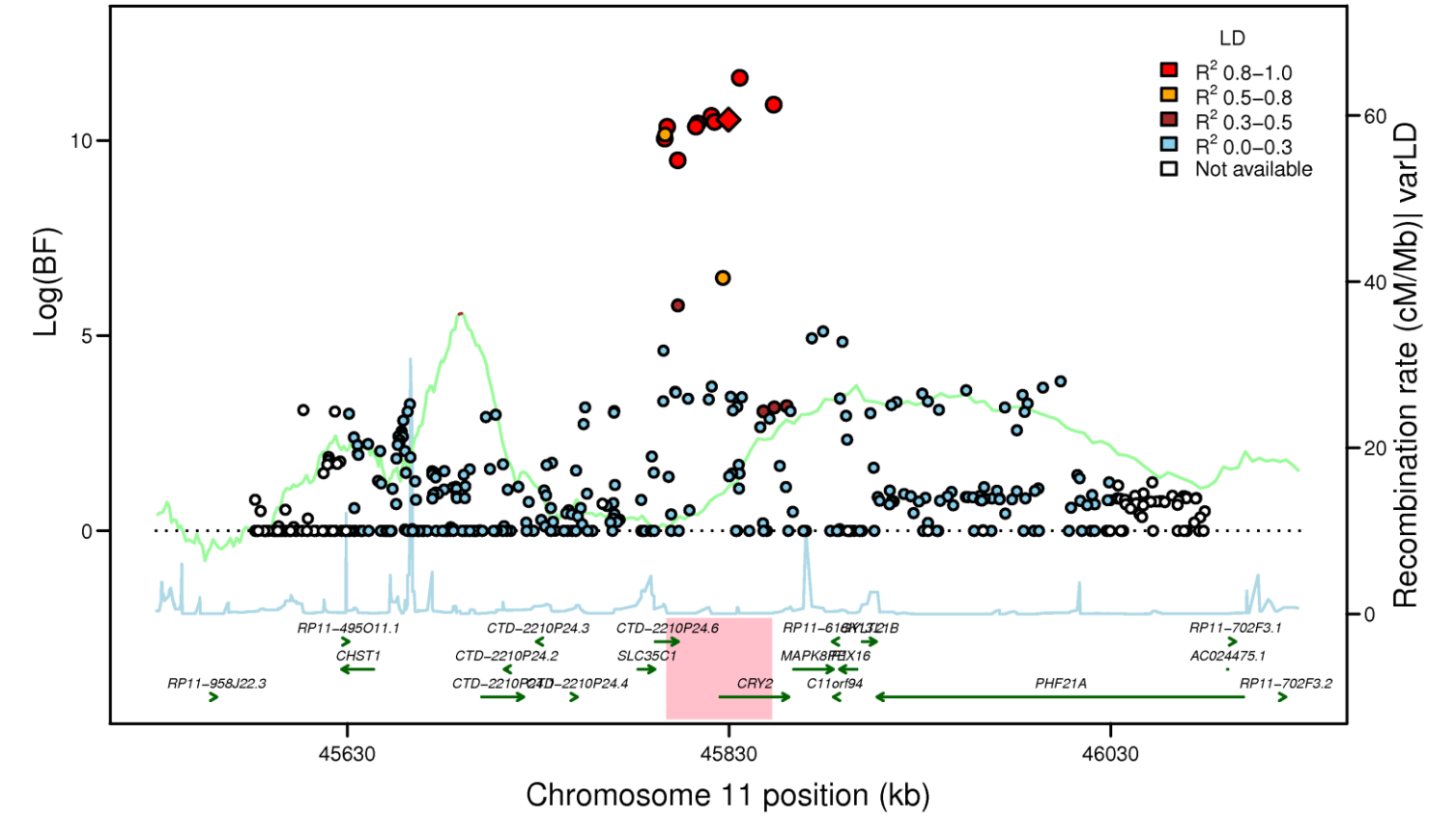
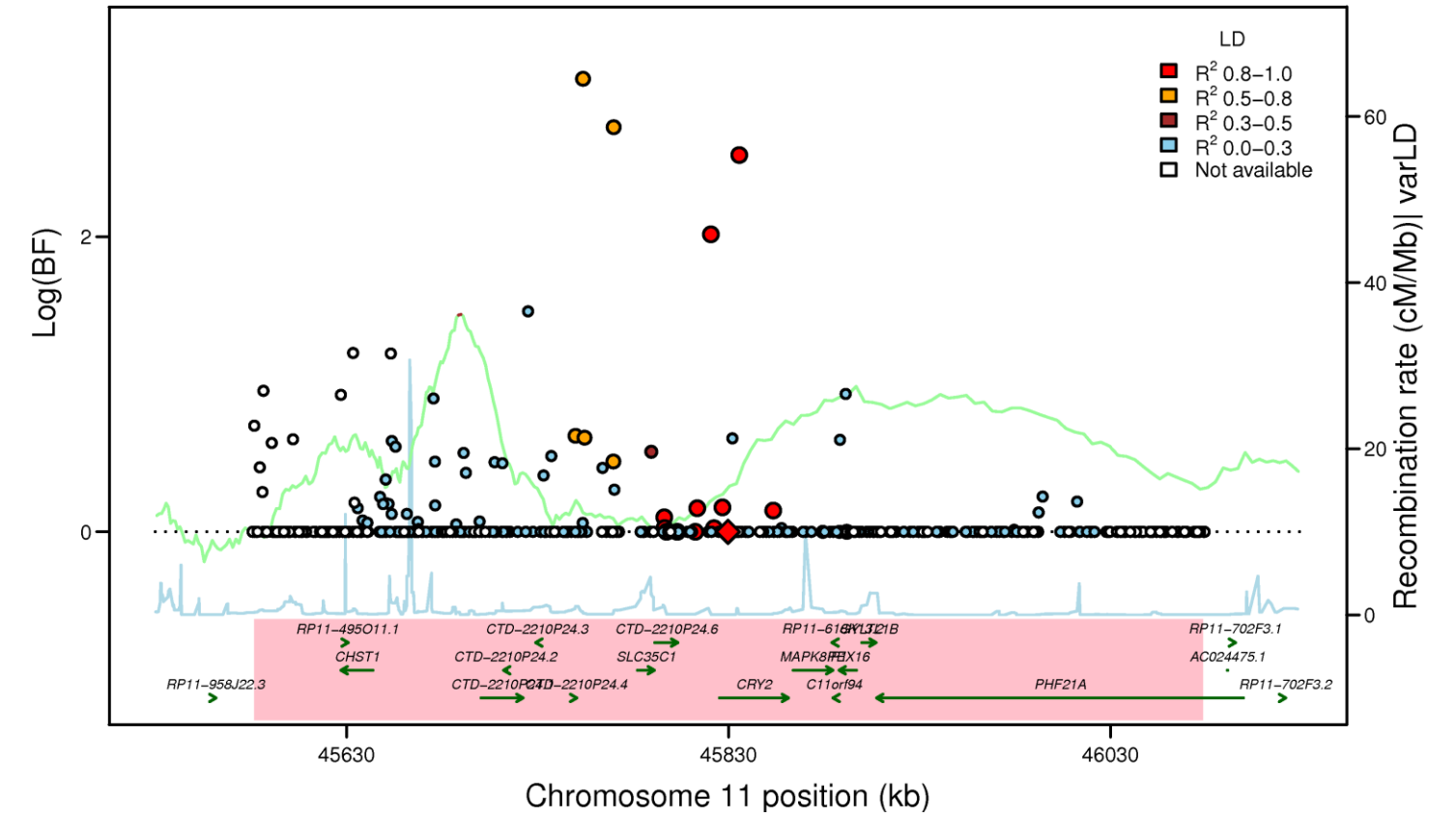


Figure S3N

CRY2: rs11605924 (FG EA_MANTRA, LD: HapMap2 CEU)



CRY2: rs11605924 (FG AA_MANTRA, LD: HapMap2 YRI)



CRY2: rs11605924 (FG TE_MANTRA, LD: HapMap2 YRI)

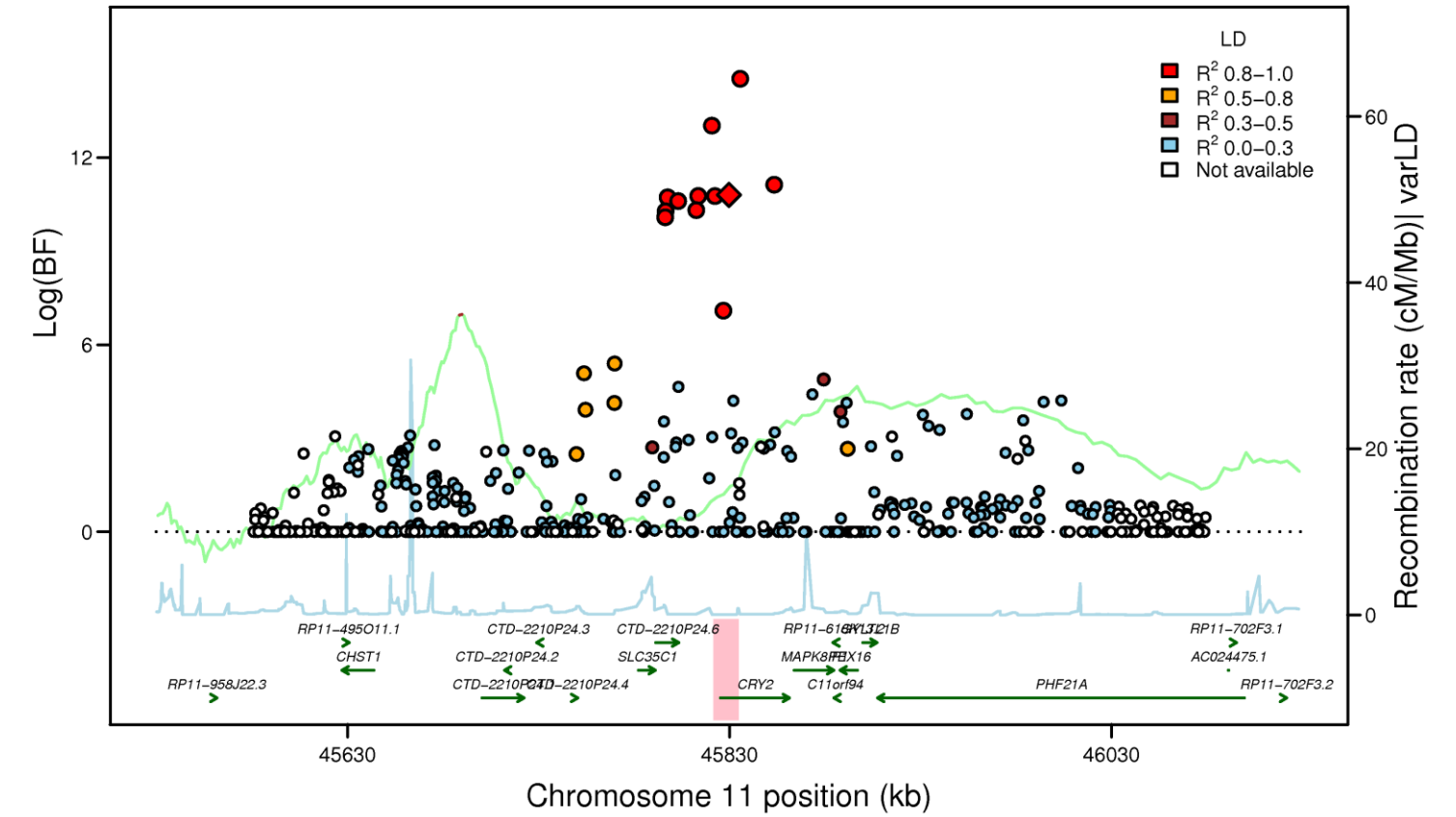
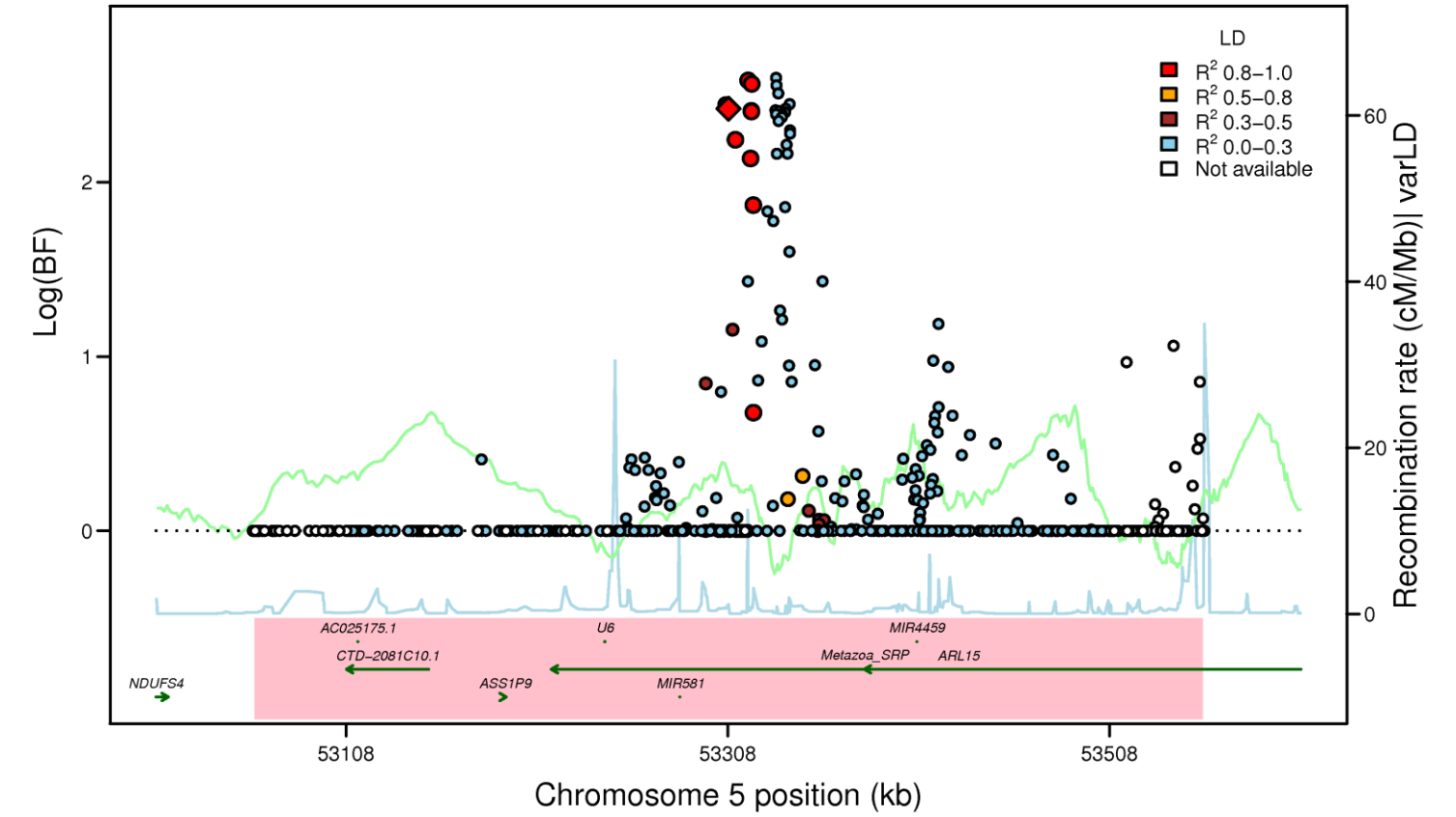
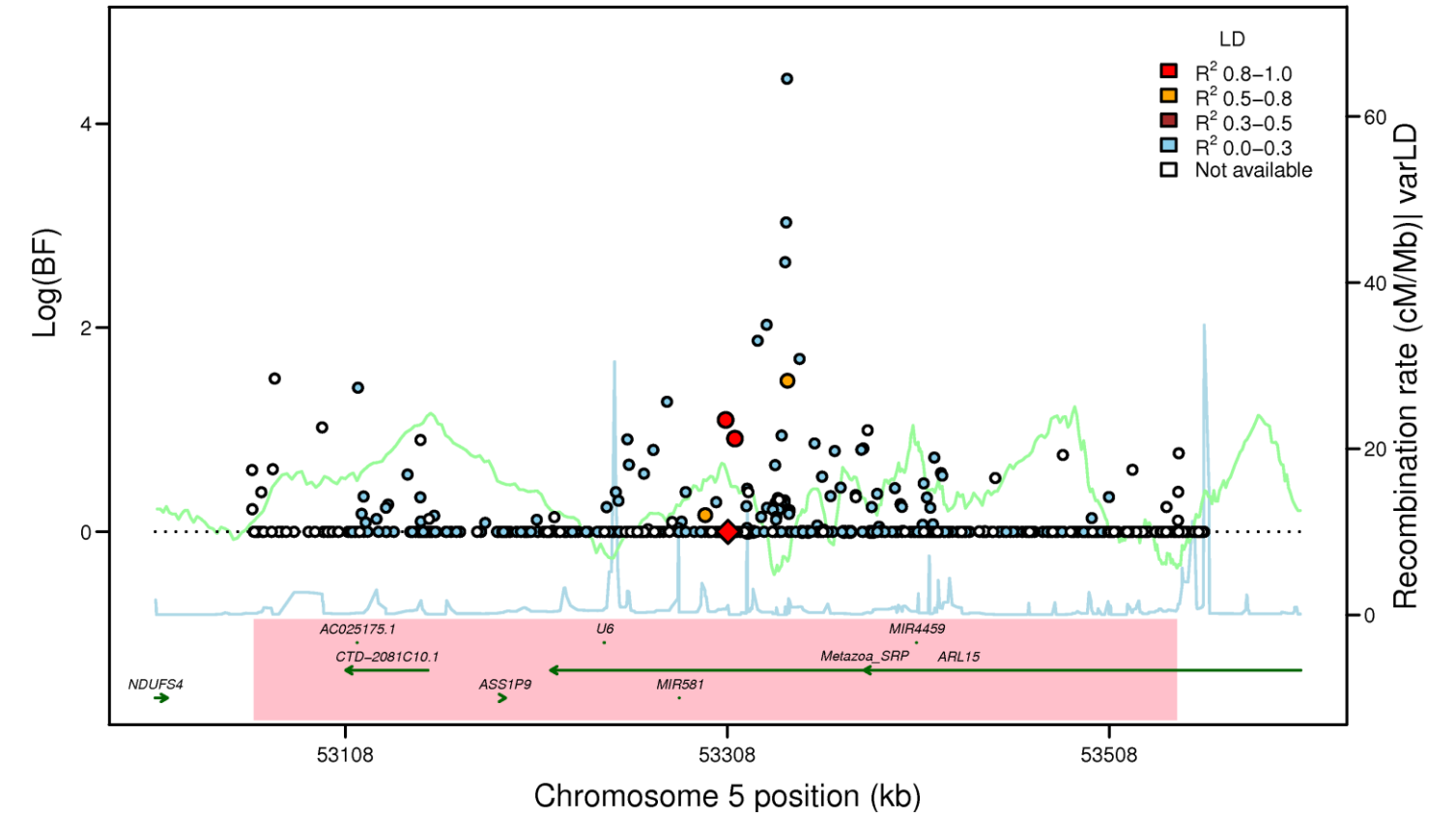


Figure S30

ARL15: rs4865796 (FI EA_MANTRA, LD: HapMap2 CEU)



ARL15: rs4865796 (FI AA_MANTRA, LD: HapMap2 YRI)



ARL15: rs4865796 (FI TE_MANTRA, LD: HapMap2 YRI)

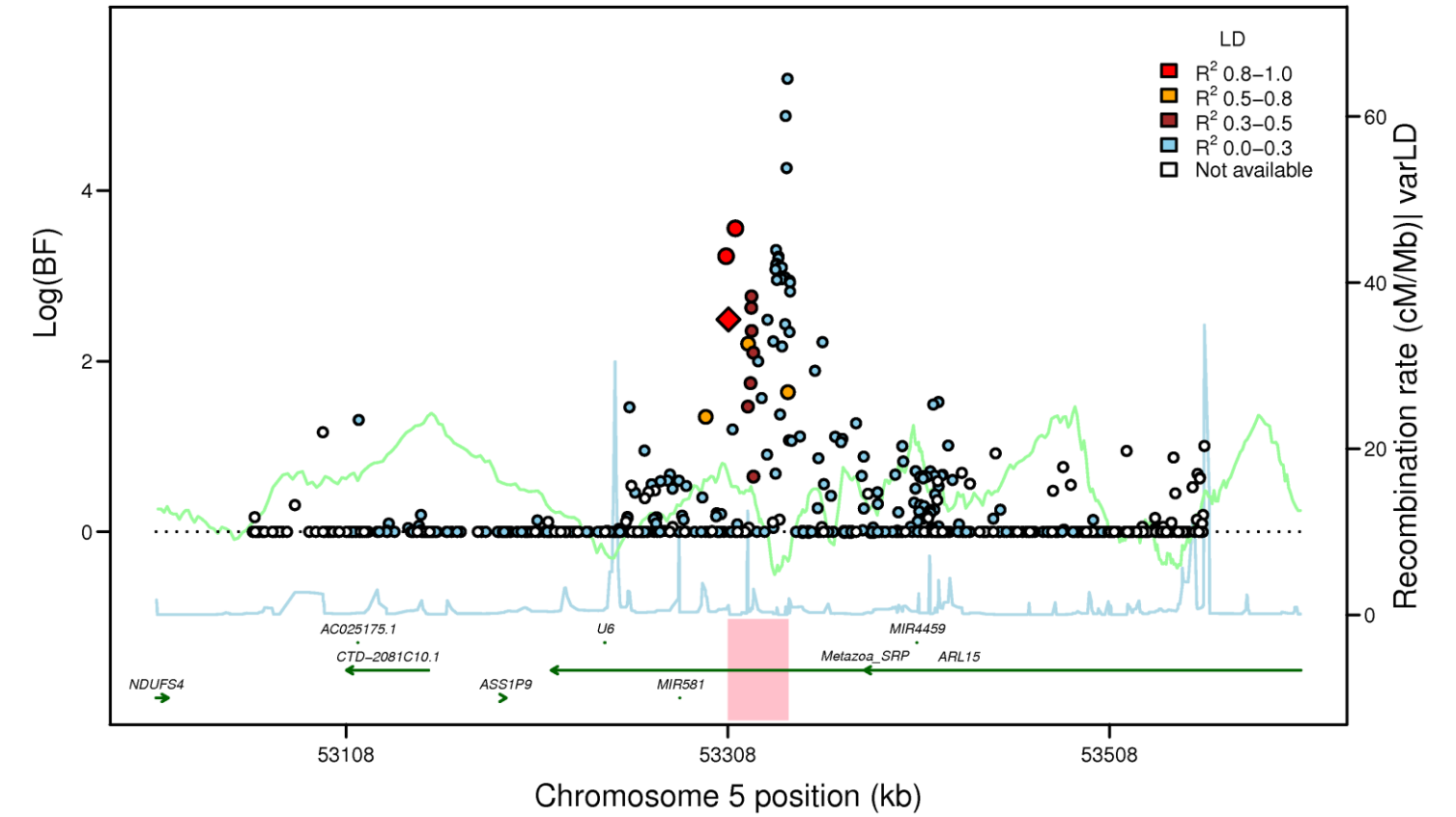
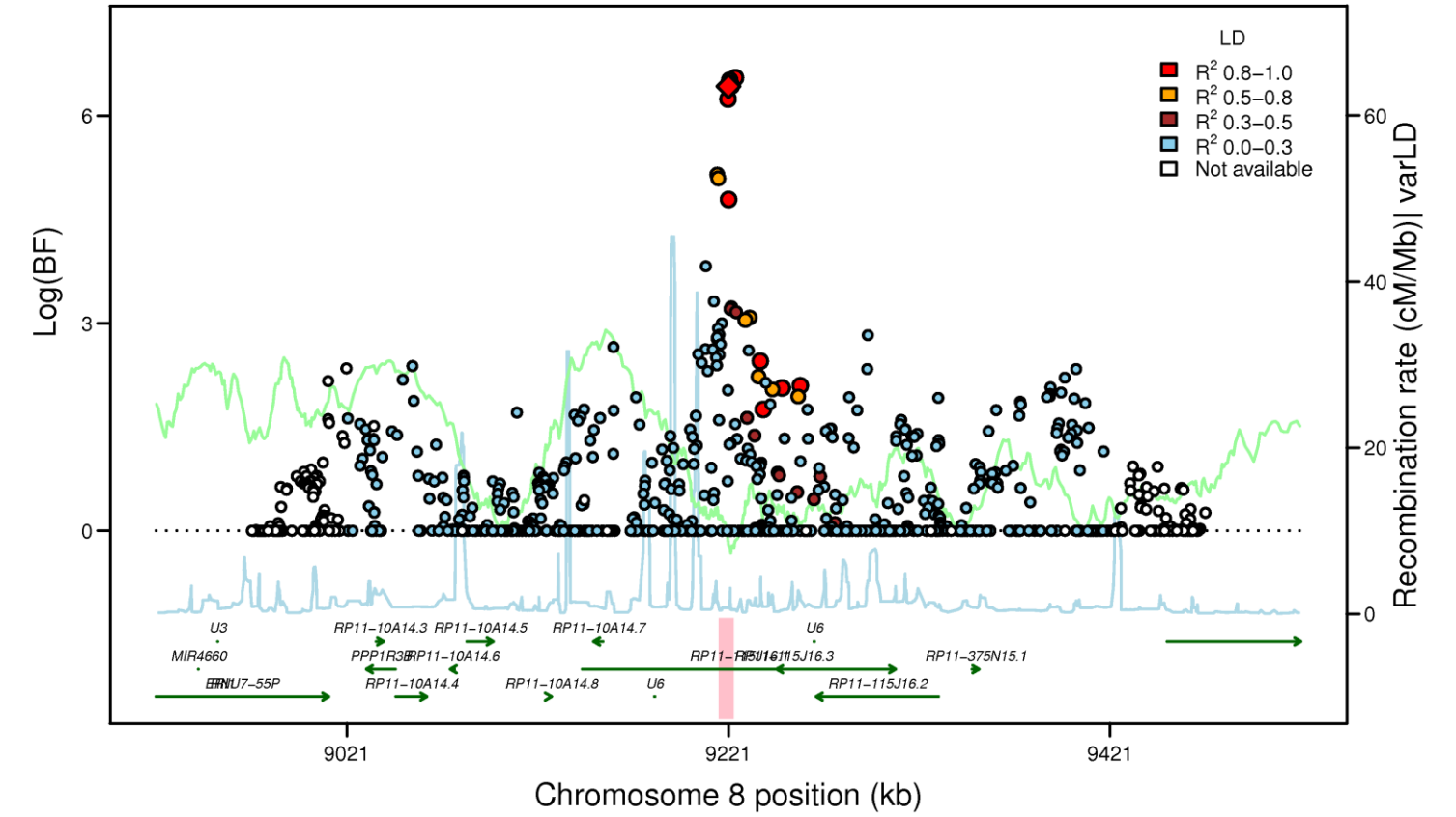
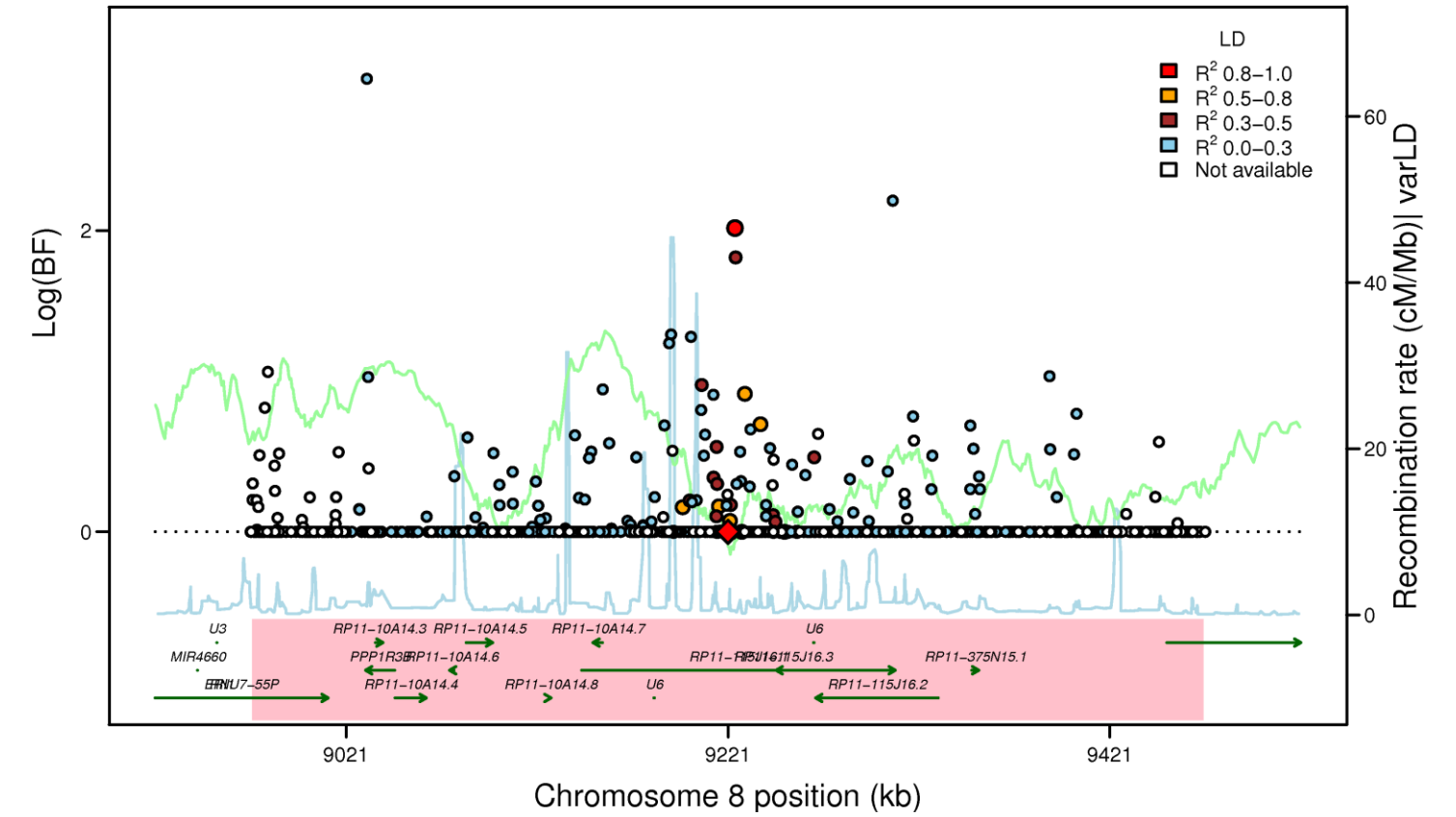


Figure S3P

PPP1R3B: rs4841132 (FI EA_MANTRA, LD: HapMap2 CEU)



PPP1R3B: rs4841132 (FI AA_MANTRA, LD: HapMap2 YRI)



PPP1R3B: rs4841132 (FI TE_MANTRA, LD: HapMap2 YRI)

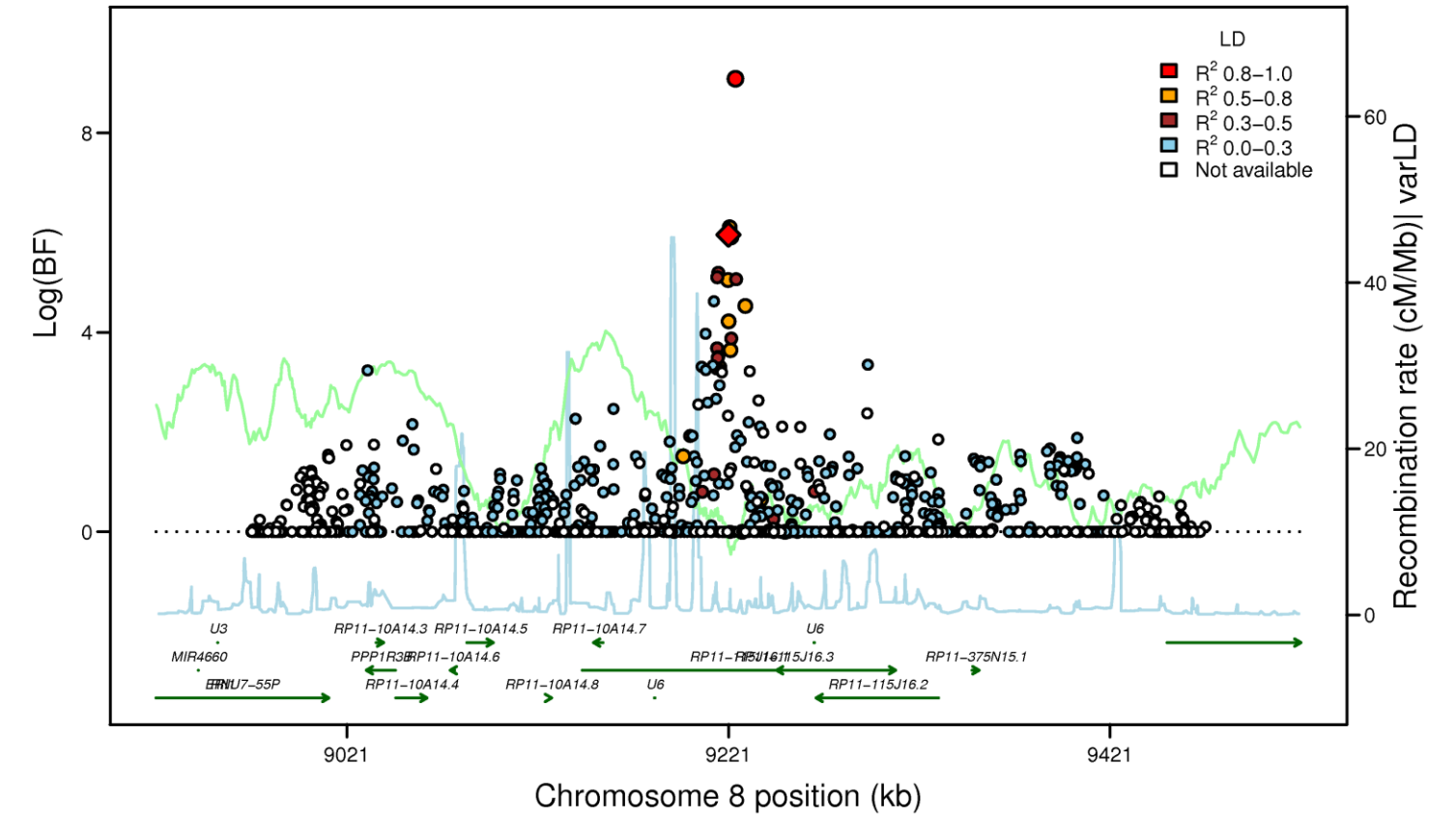
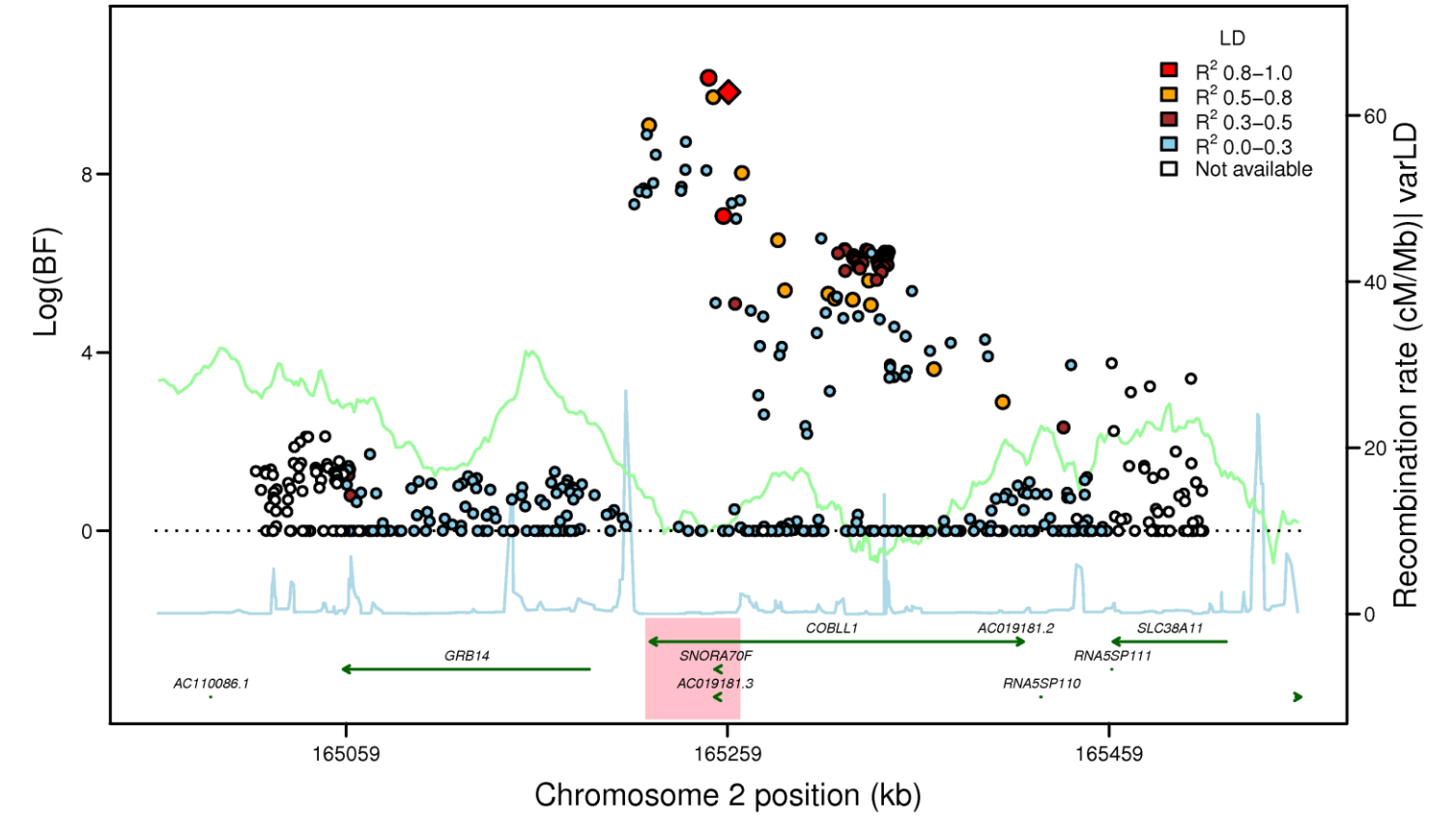
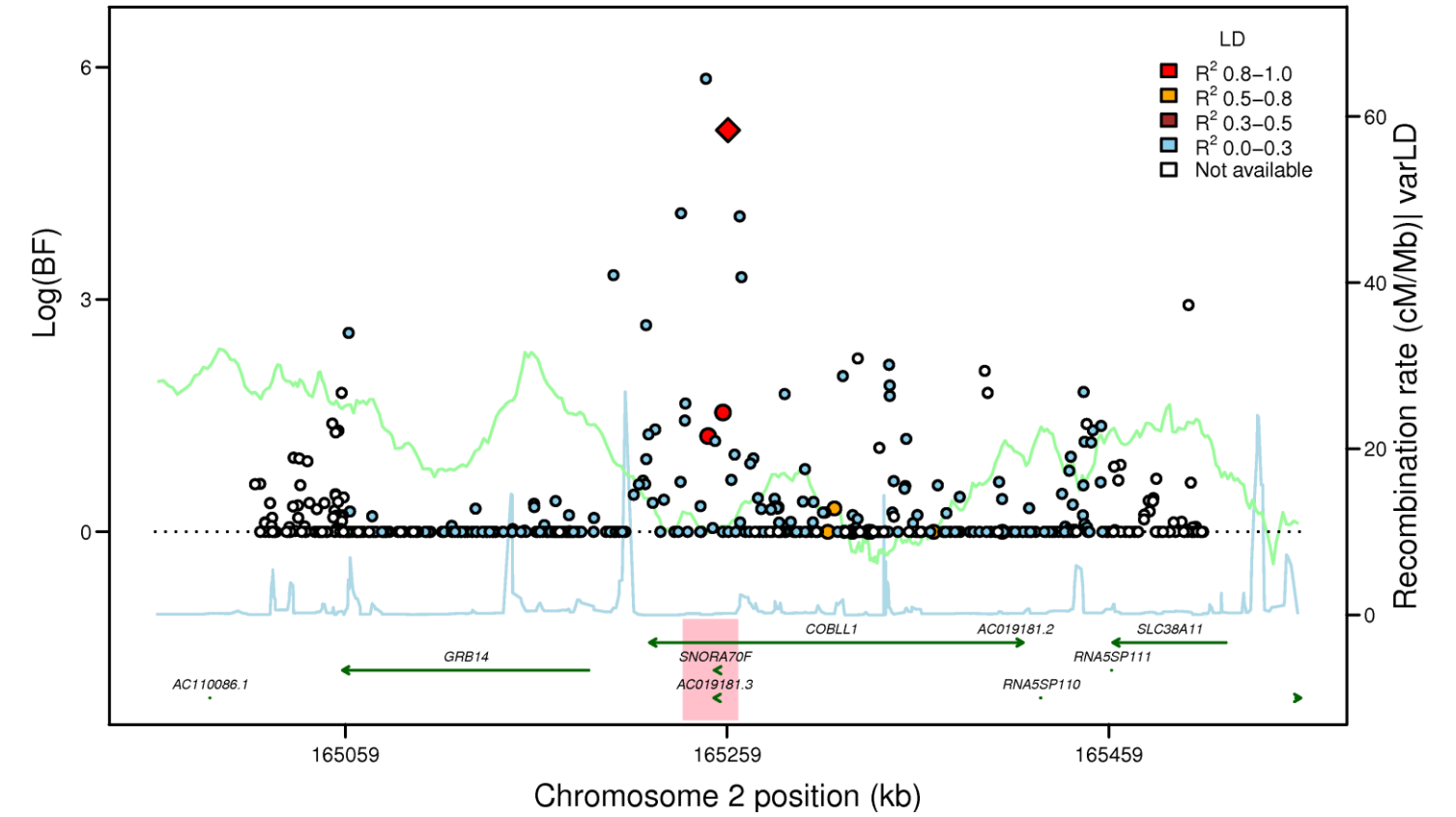


Figure S3Q

COBLL1–GRB14: rs7607980 (FI EA_MANTRA, LD: HapMap2 CEU)



COBLL1–GRB14: rs7607980 (FI AA_MANTRA, LD: HapMap2 YRI)



COBLL1–GRB14: rs7607980 (FI TE_MANTRA, LD: HapMap2 YRI)

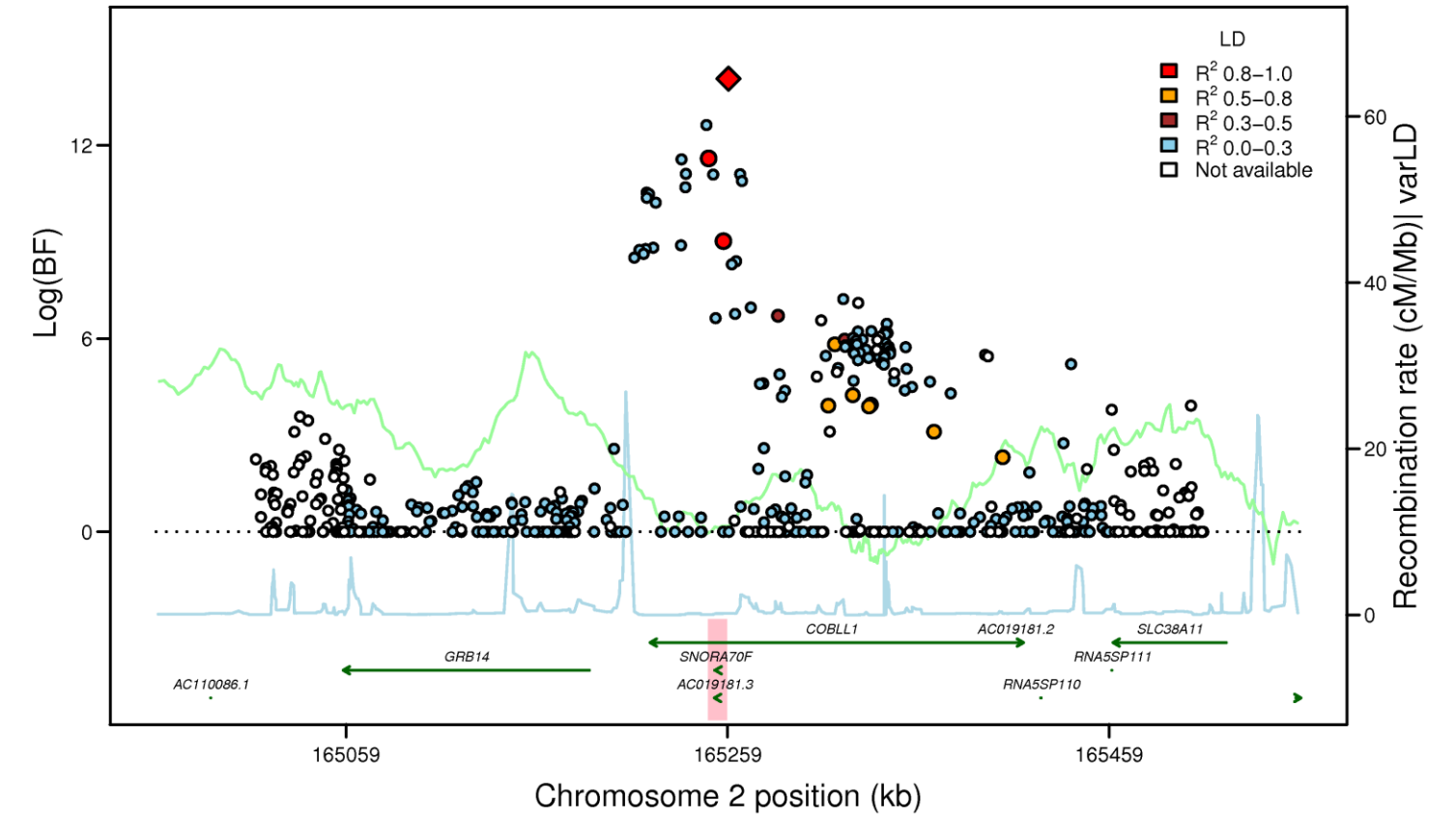
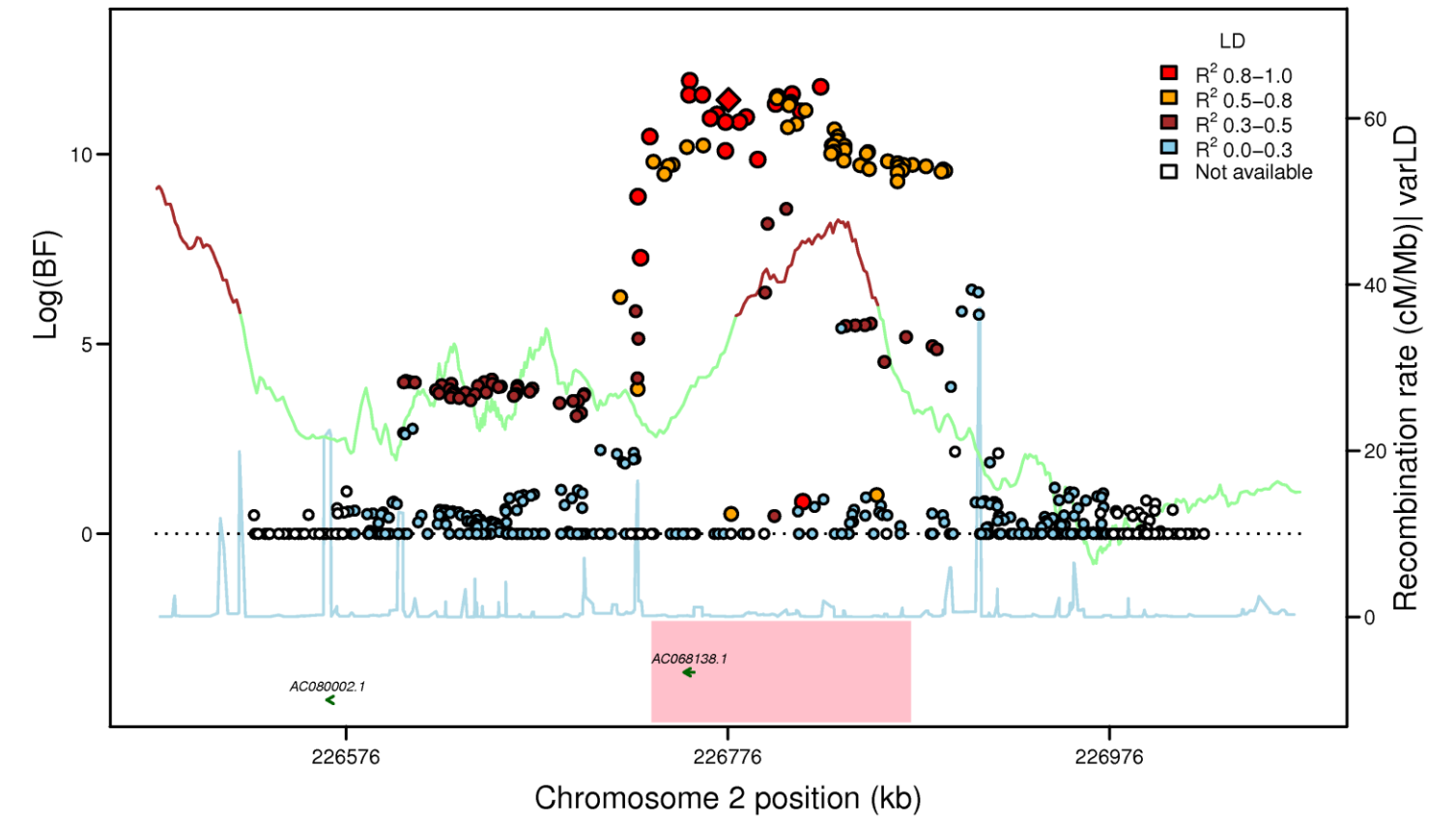
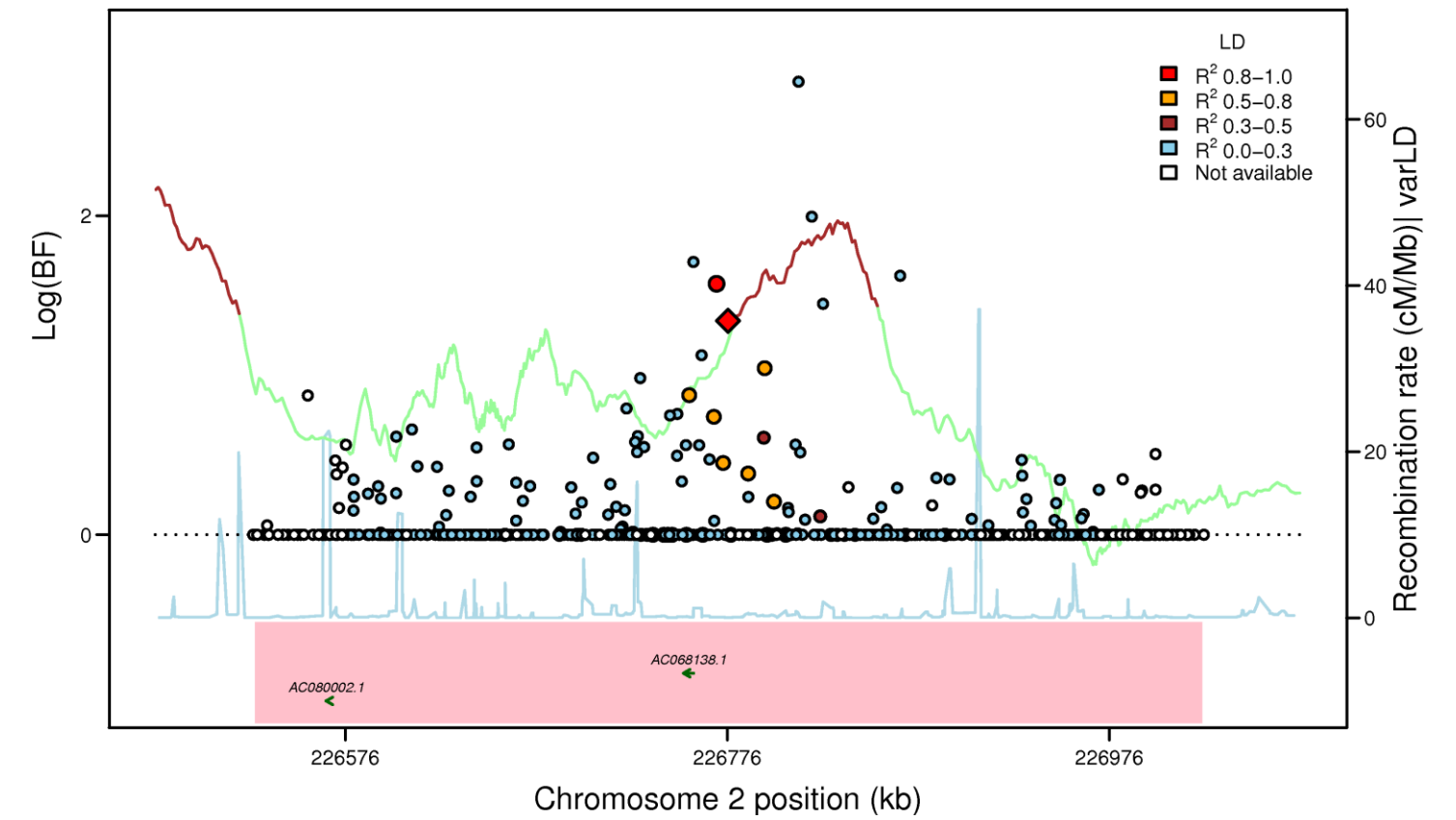


Figure S3R

IRS1: rs2943634 (FI EA_MANTRA, LD: HapMap2 CEU)



IRS1: rs2943634 (FI AA_MANTRA, LD: HapMap2 YRI)



IRS1: rs2943634 (FI TE_MANTRA, LD: HapMap2 YRI)

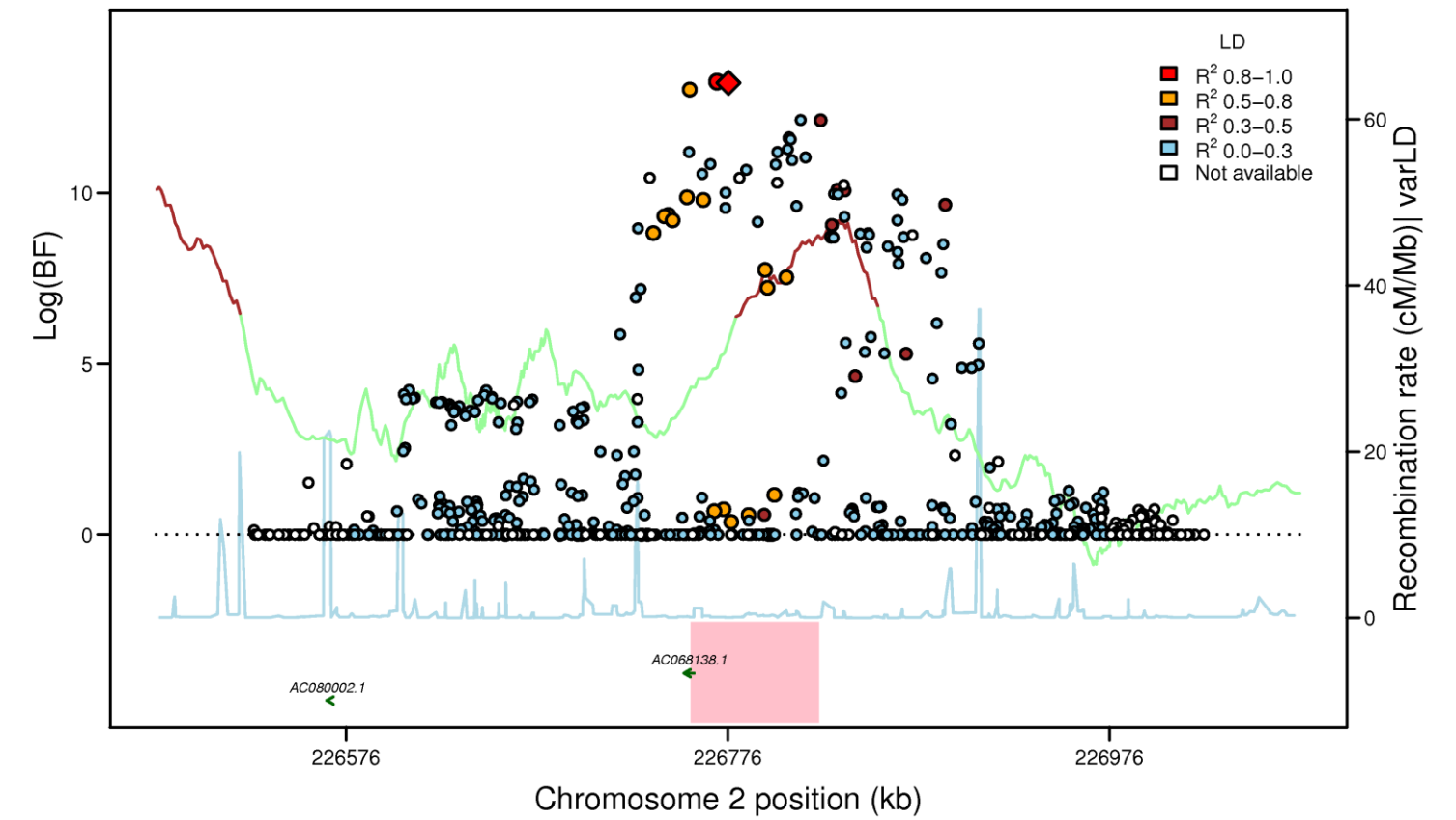
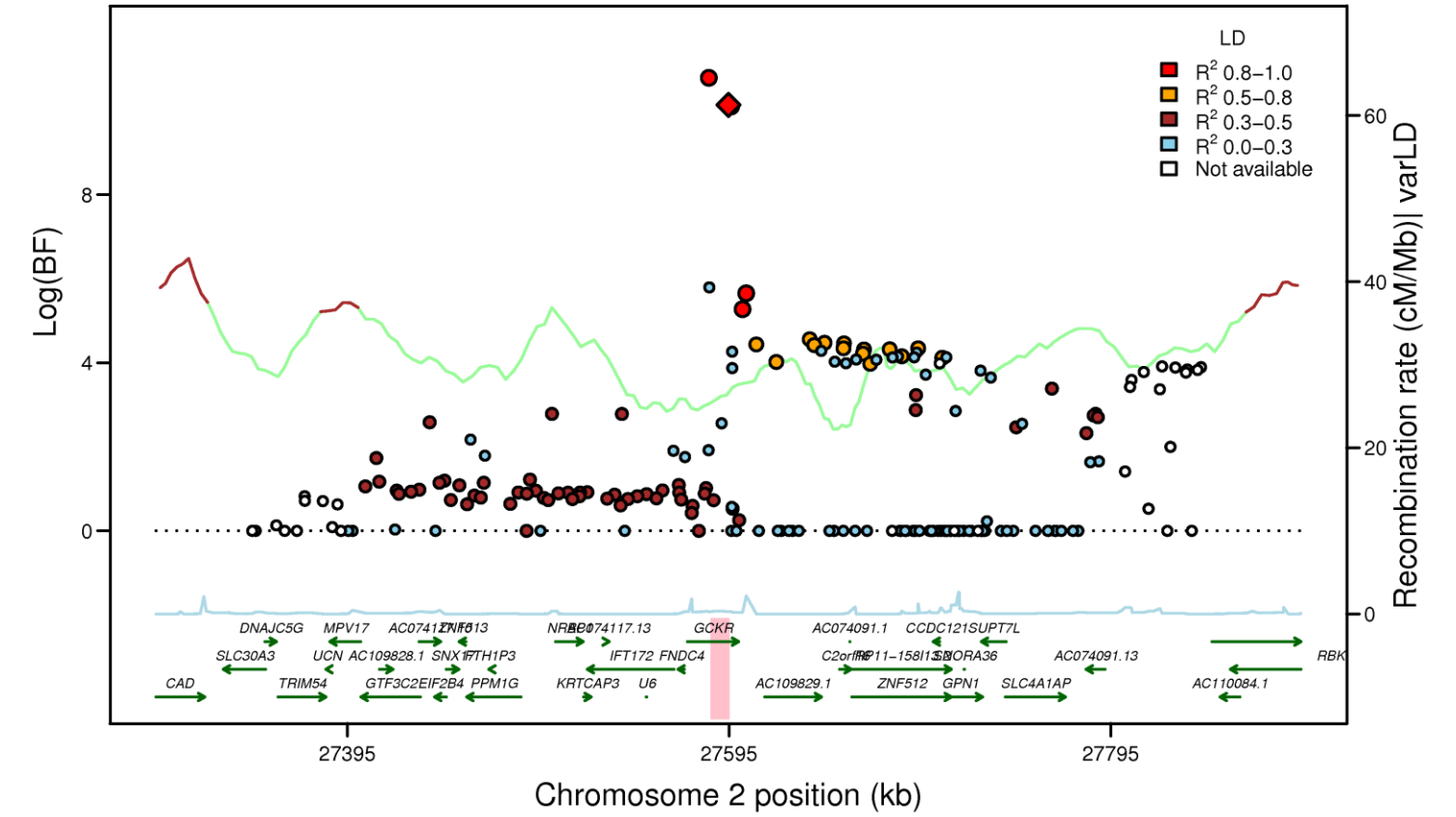
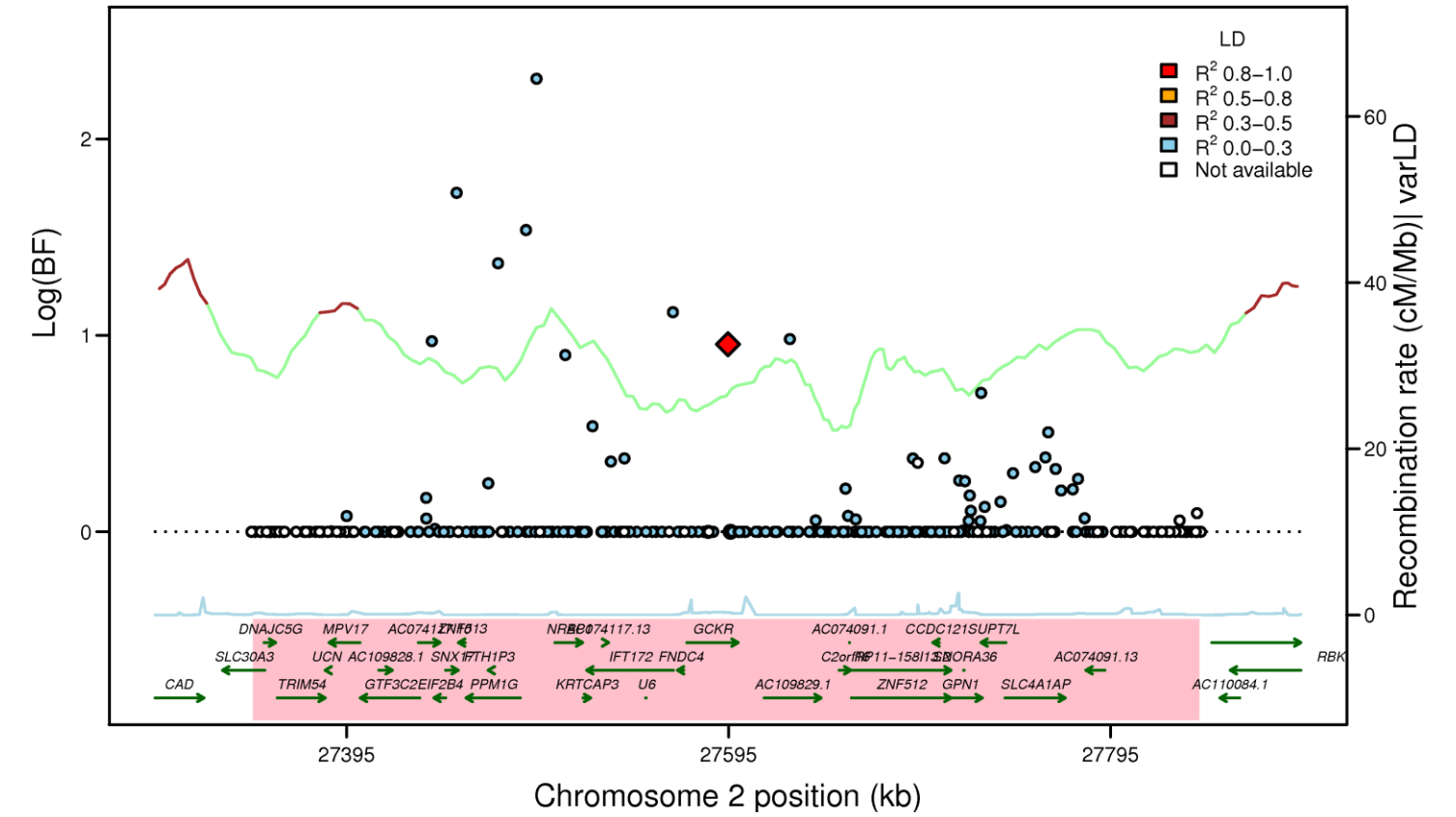


Figure S3S

GCKR: rs780094 (FI EA_MANTRA, LD: HapMap2 CEU)



GCKR: rs780094 (FI AA_MANTRA, LD: HapMap2 YRI)



GCKR: rs780094 (FI TE_MANTRA, LD: HapMap2 YRI)

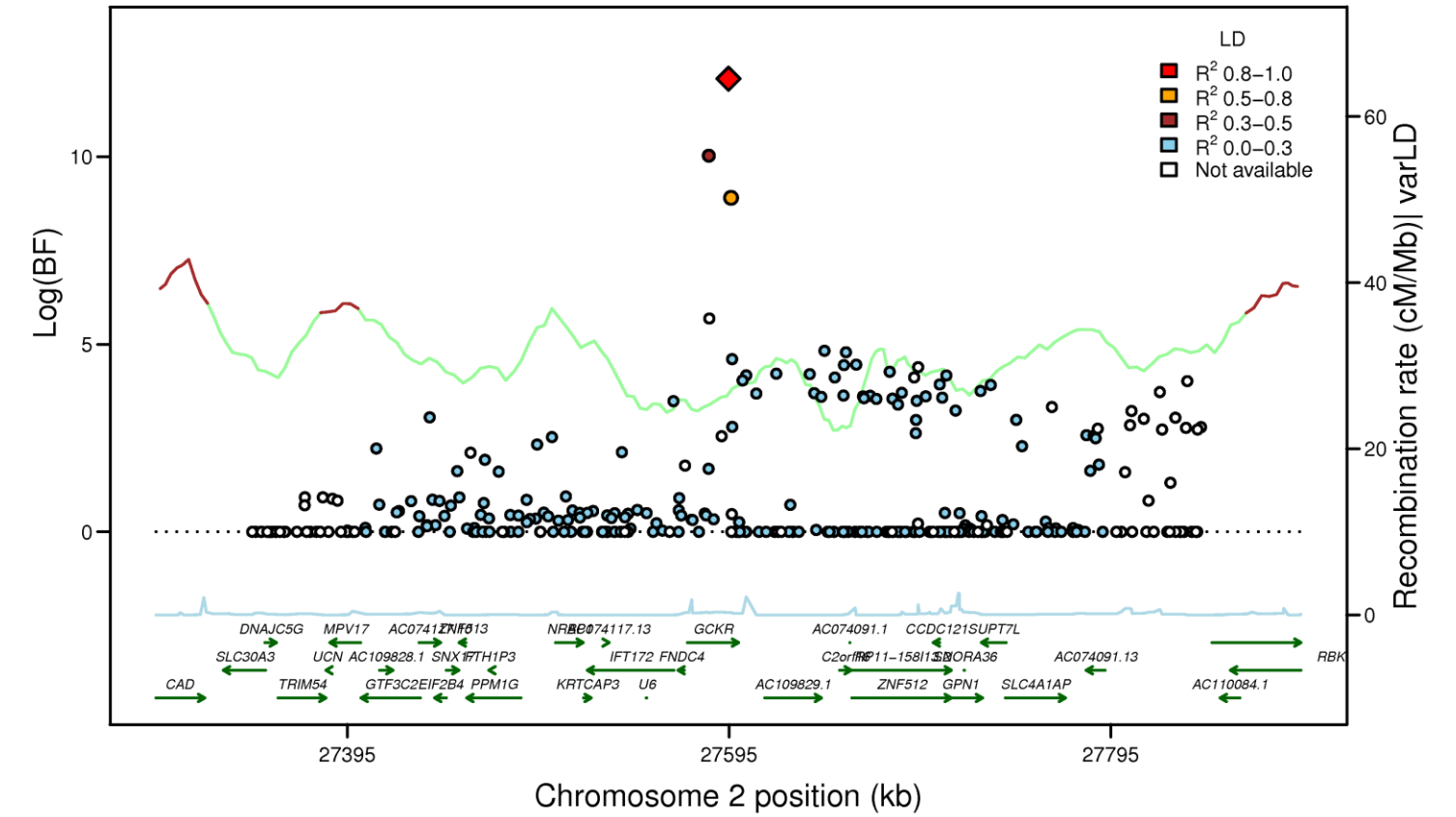
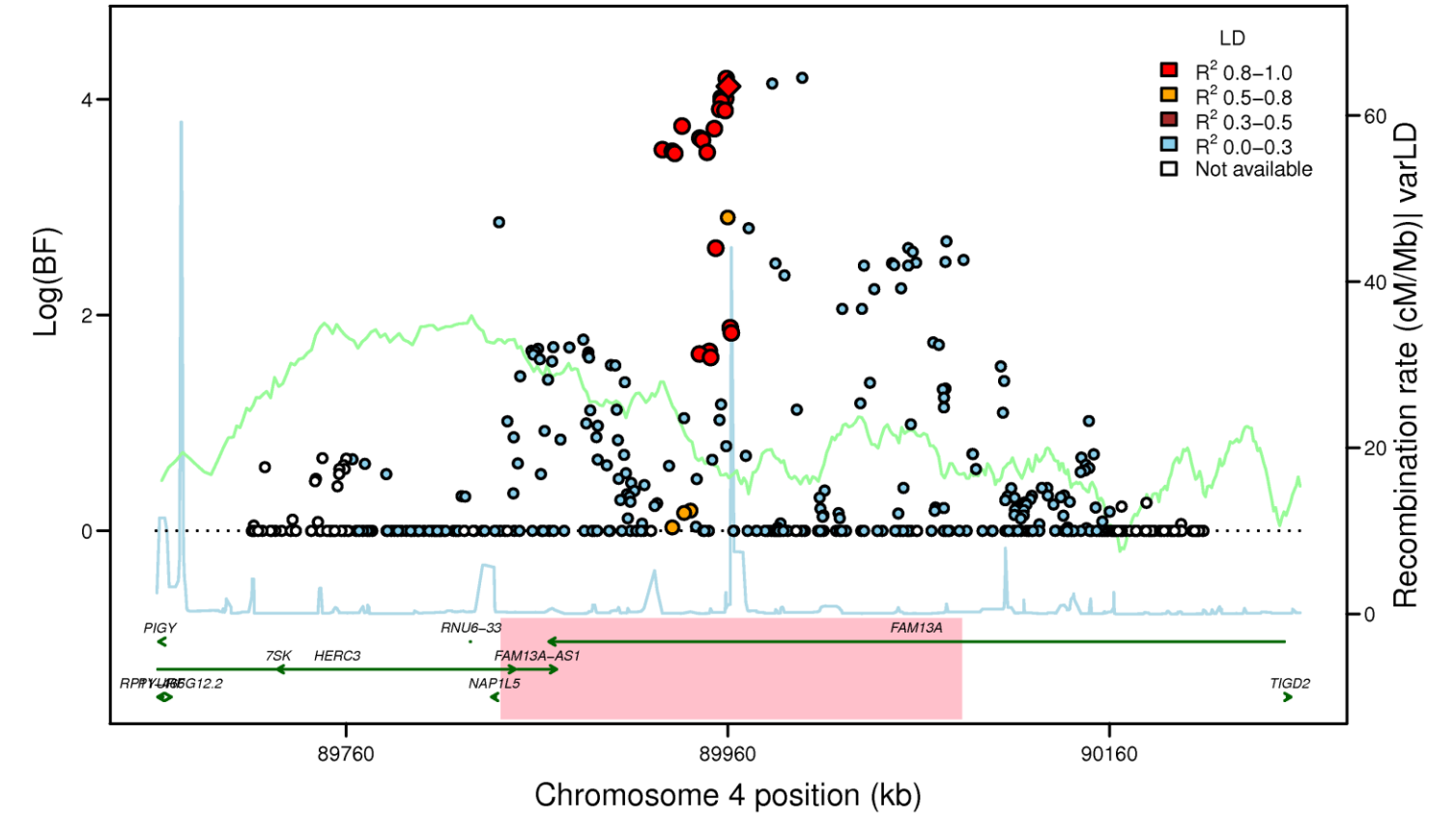
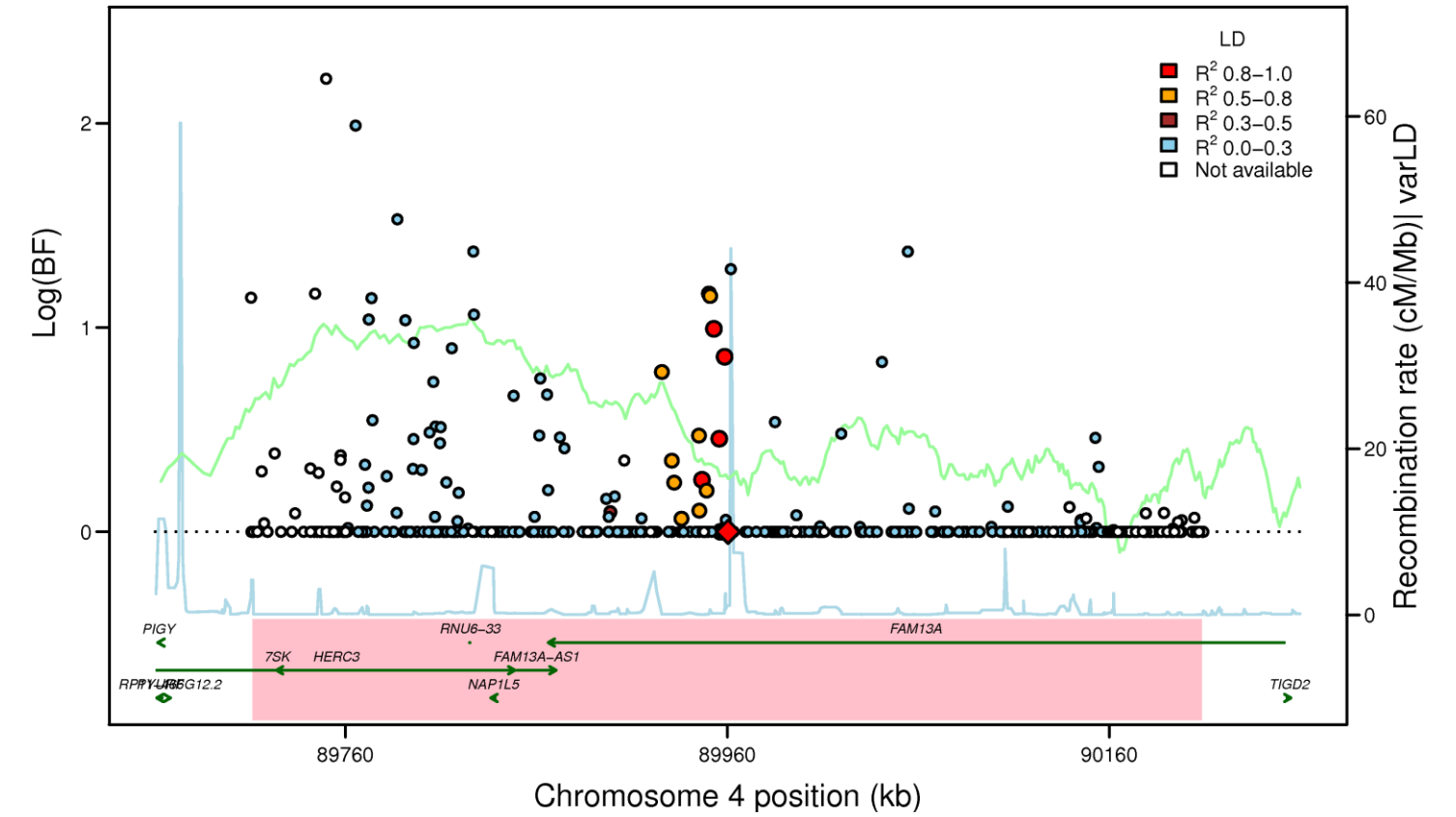


Figure S3T

FAM13A: rs3822072 (FI EA_MANTRA, LD: HapMap2 CEU)



FAM13A: rs3822072 (FI AA_MANTRA, LD: HapMap2 YRI)



FAM13A: rs3822072 (FI TE_MANTRA, LD: HapMap2 YRI)

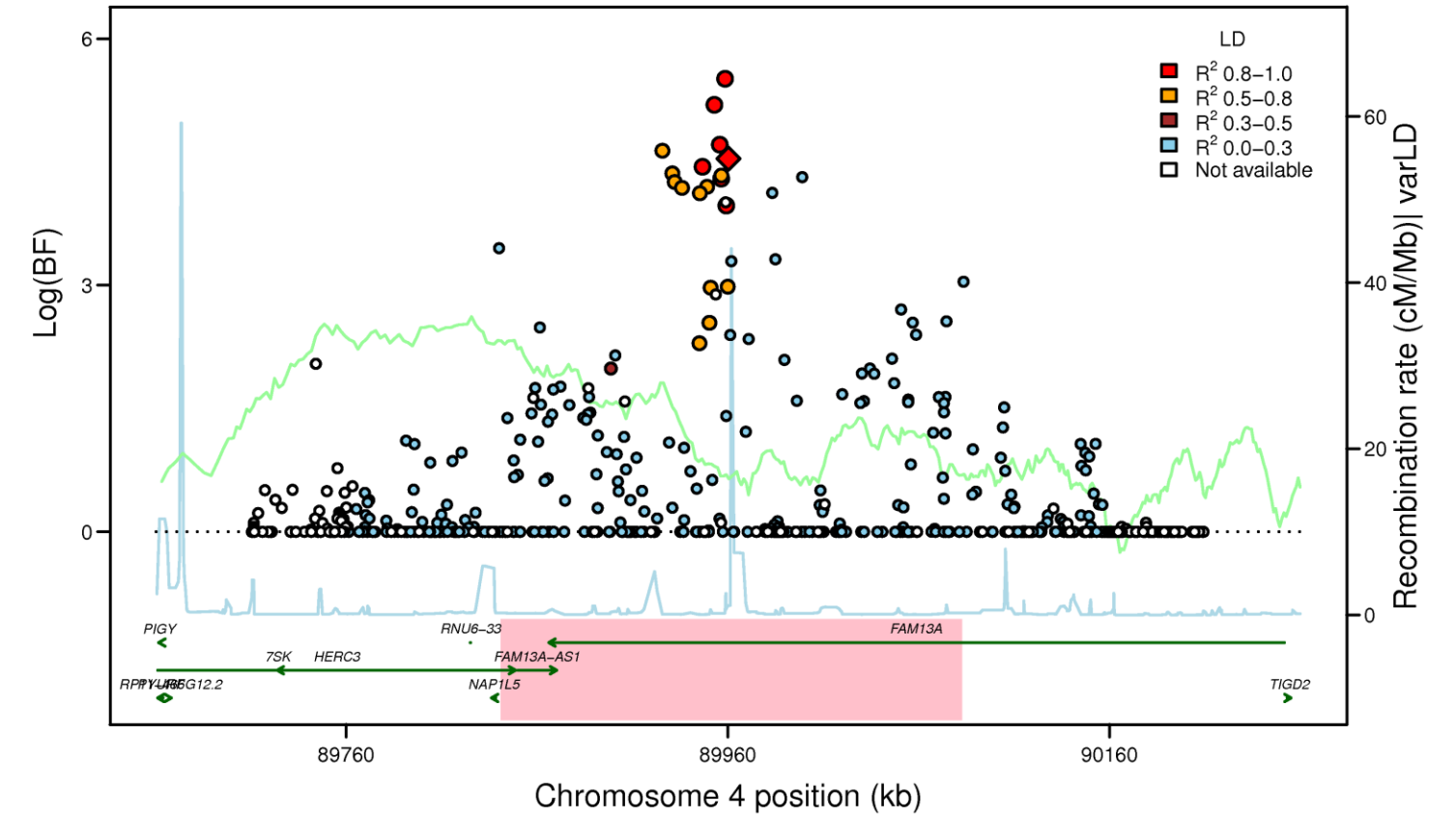
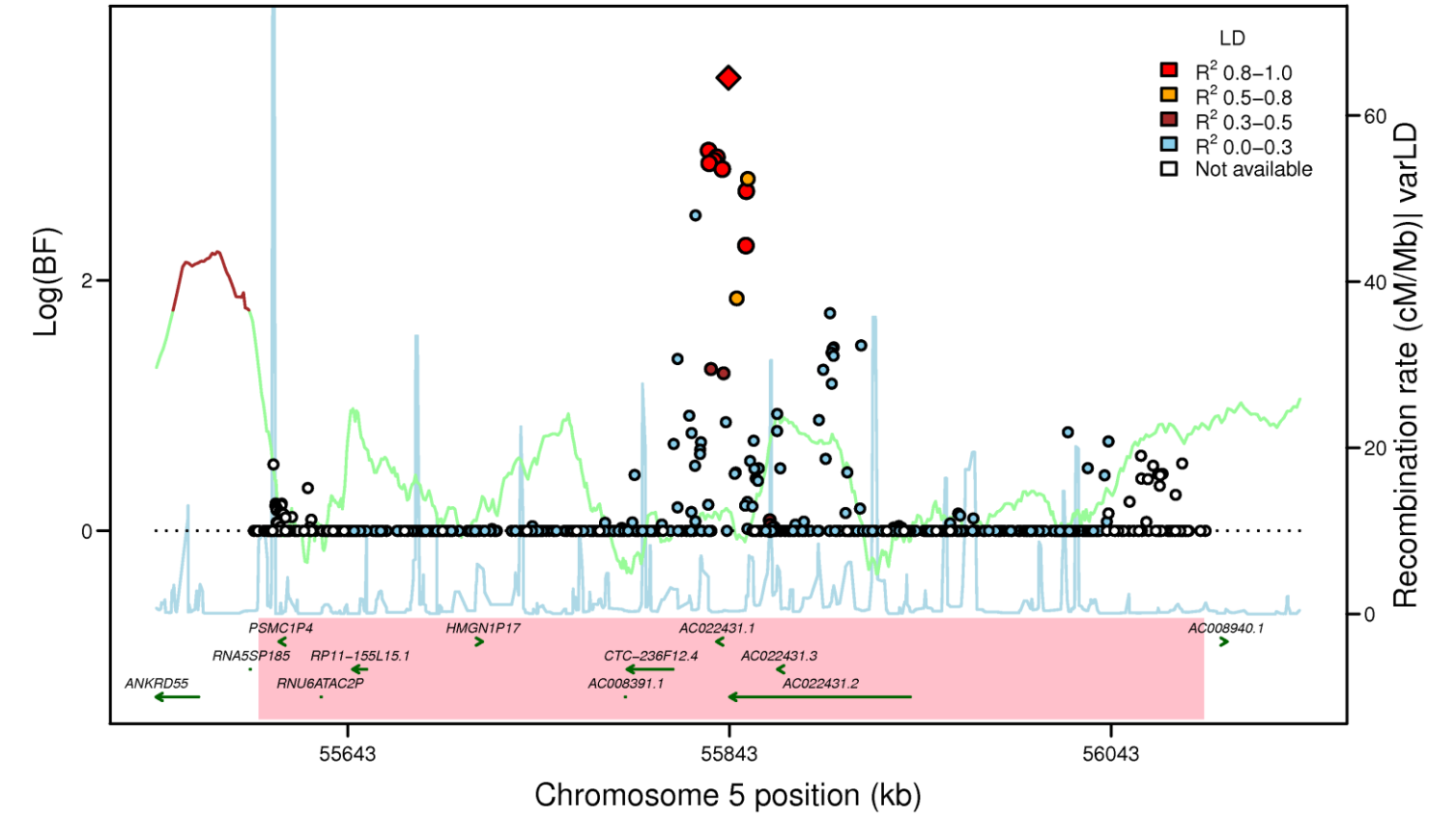
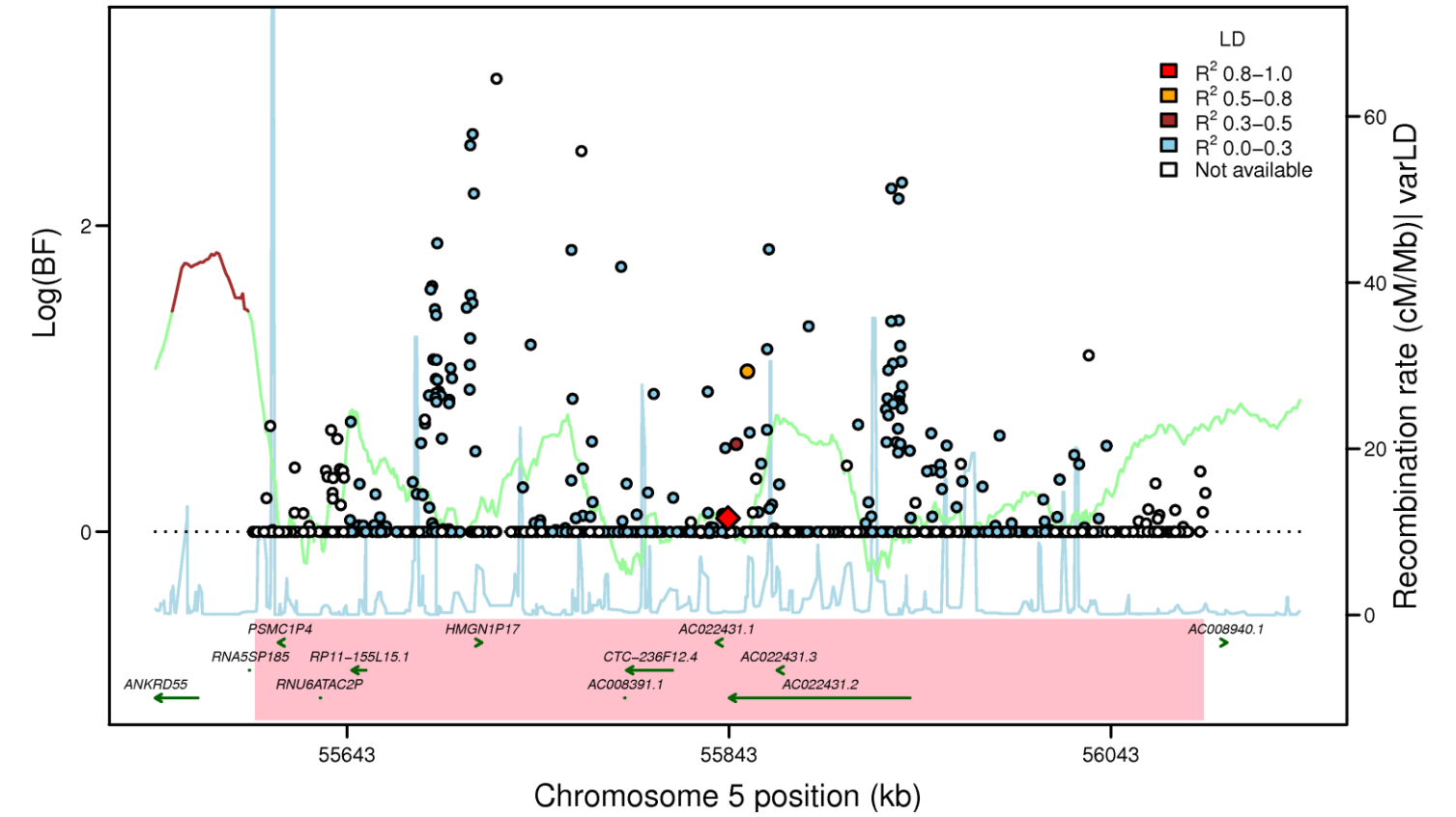


Figure S3U

ANKRD55-MAP3K1: rs459193 (FI EA_MANTRA, LD: HapMap2 CEU)



ANKRD55-MAP3K1: rs459193 (FI AA_MANTRA, LD: HapMap2 YRI)



ANKRD55-MAP3K1: rs459193 (FI TE_MANTRA, LD: HapMap2 YRI)

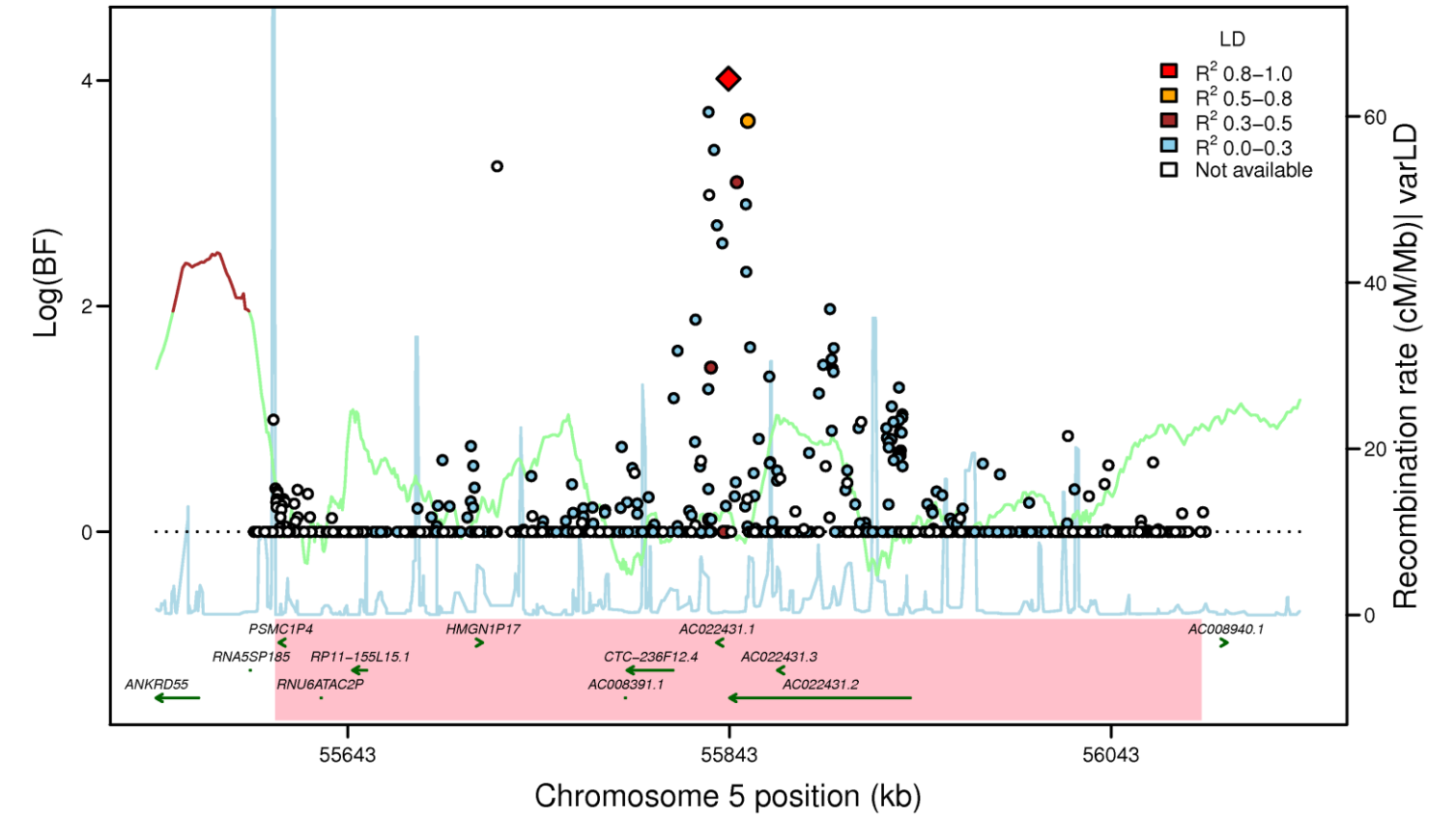
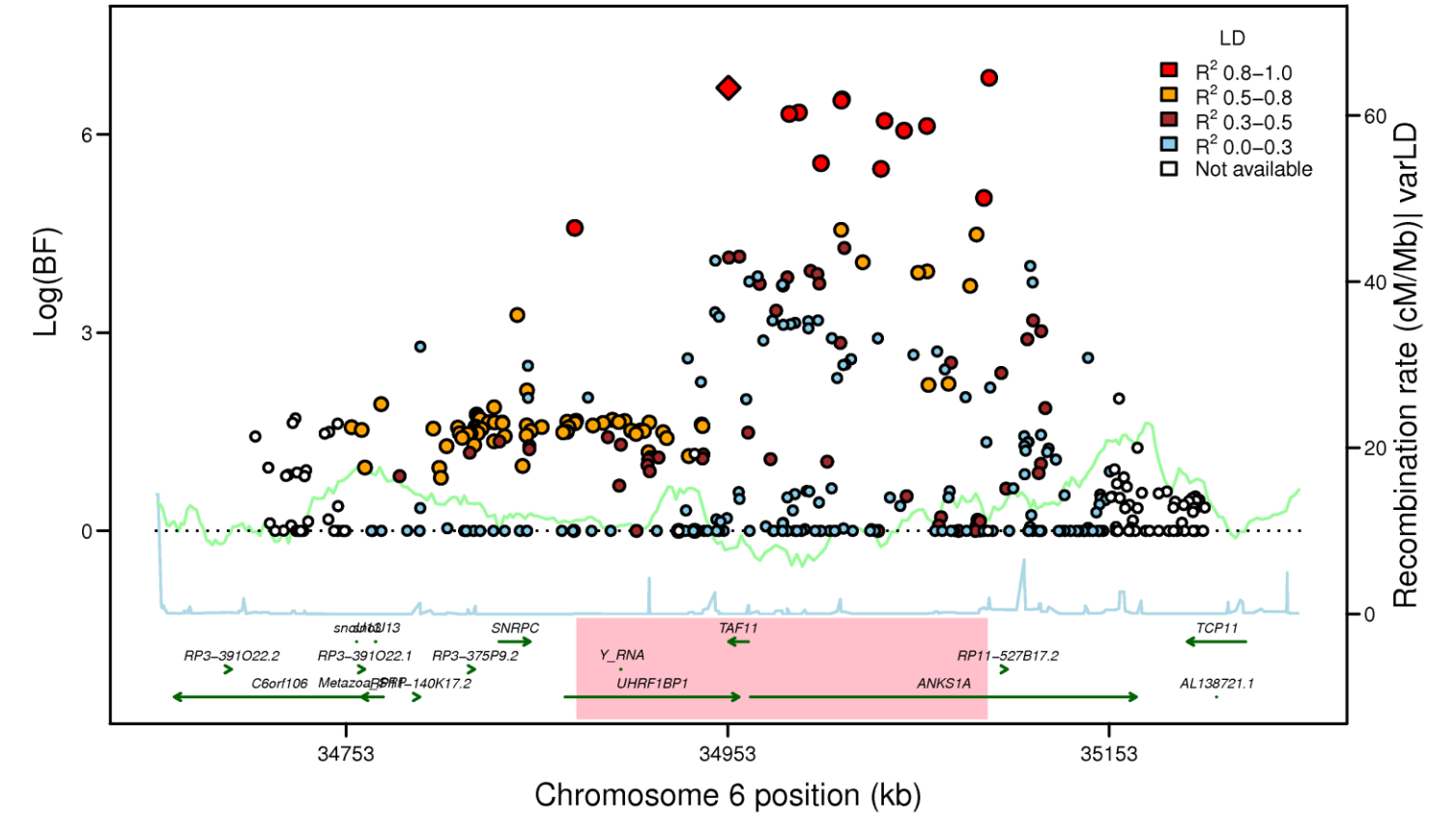
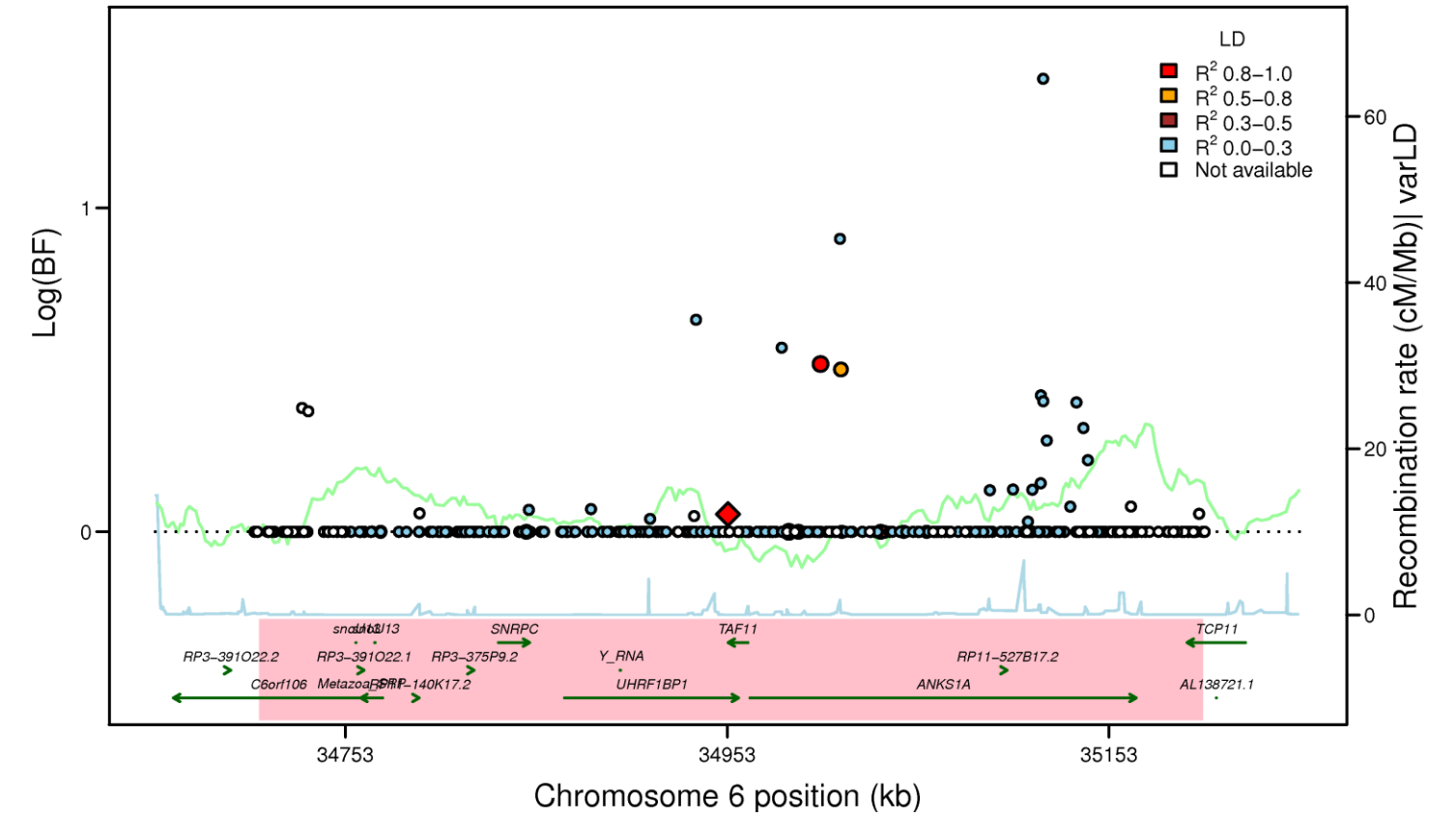


Figure S3V

UHRF1BP1: rs4646949 (FI EA_MANTRA, LD: HapMap2 CEU)



UHRF1BP1: rs4646949 (FI AA_MANTRA, LD: HapMap2 YRI)



UHRF1BP1: rs4646949 (FI TE_MANTRA, LD: HapMap2 YRI)

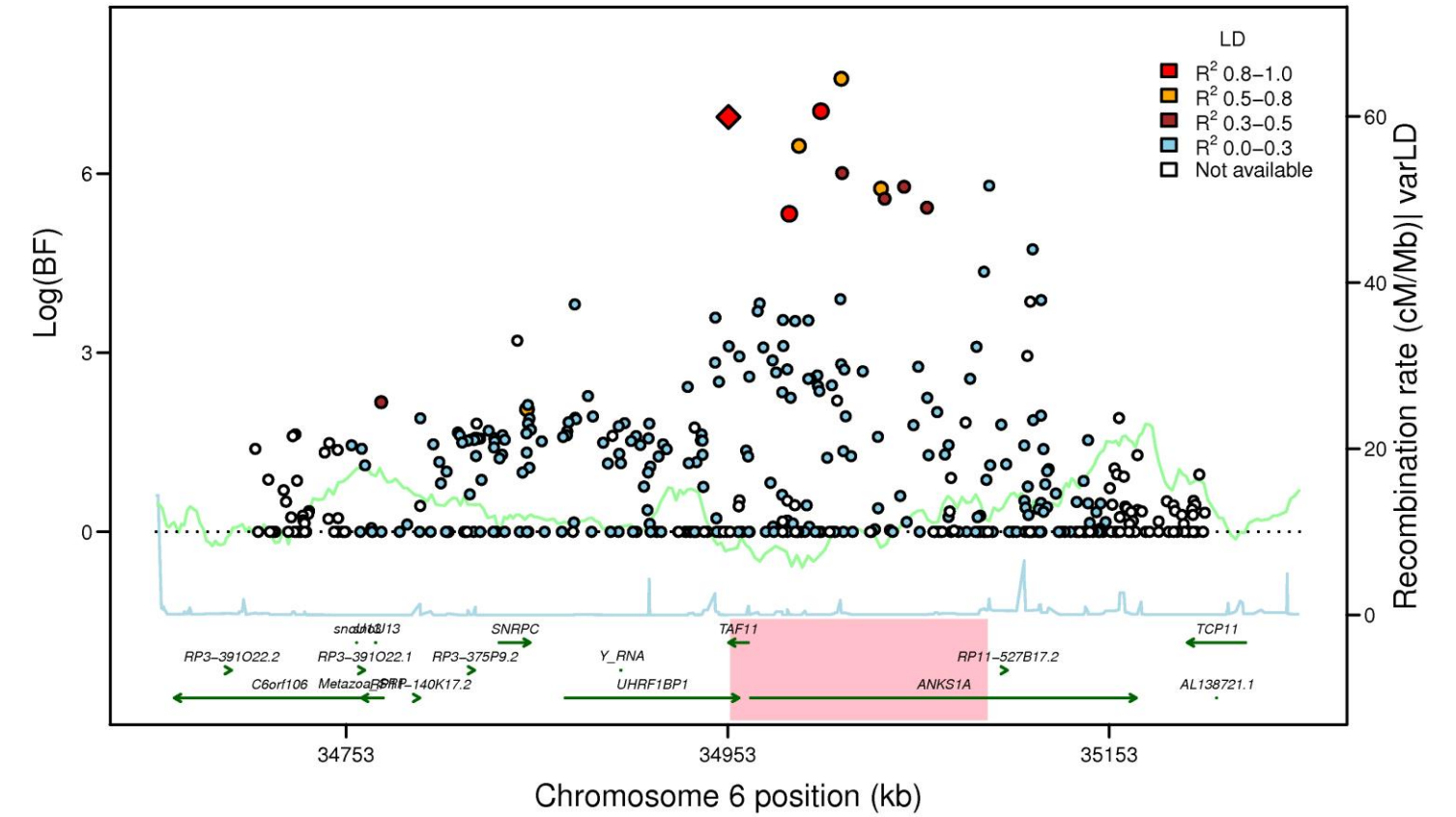
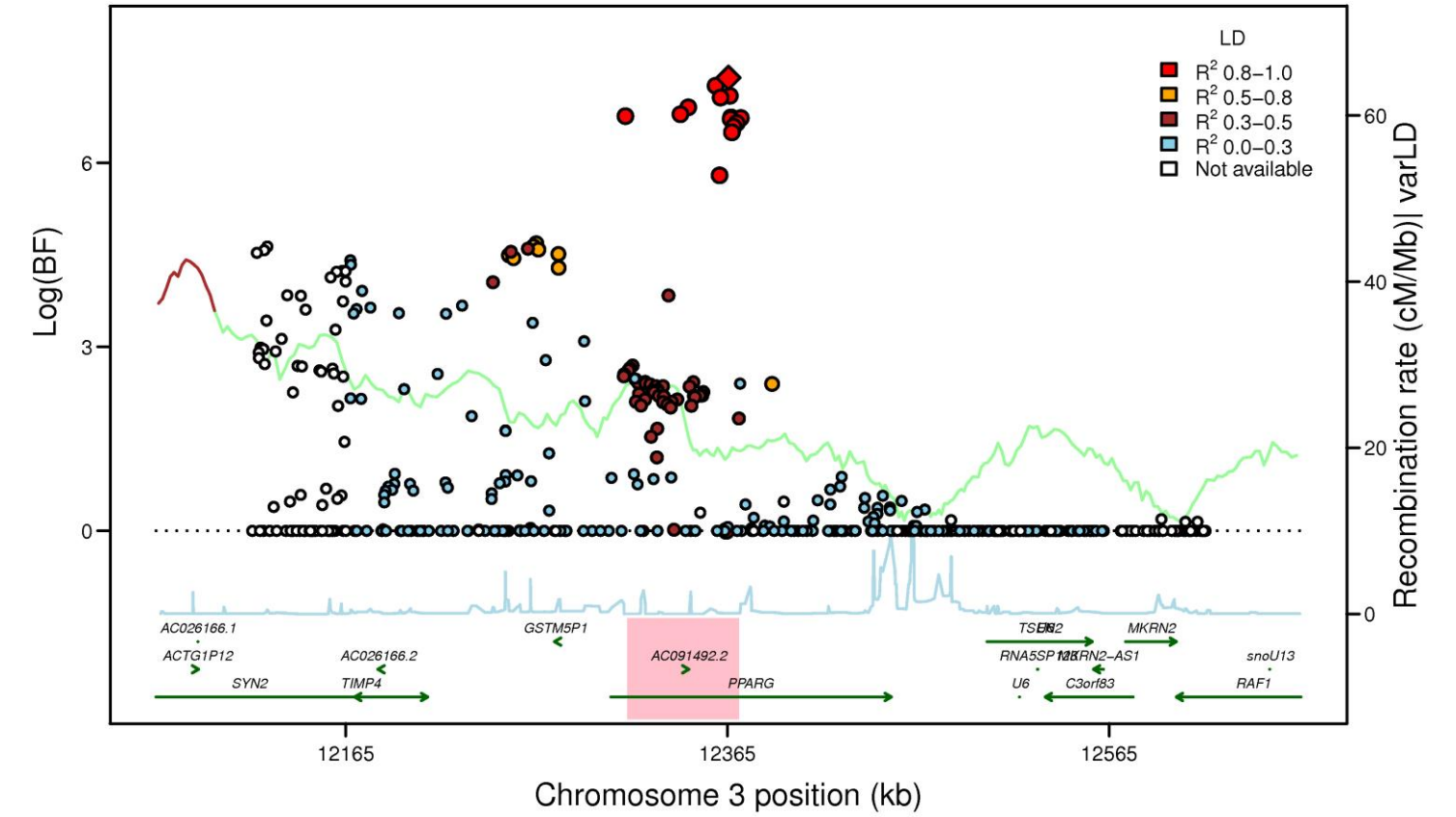
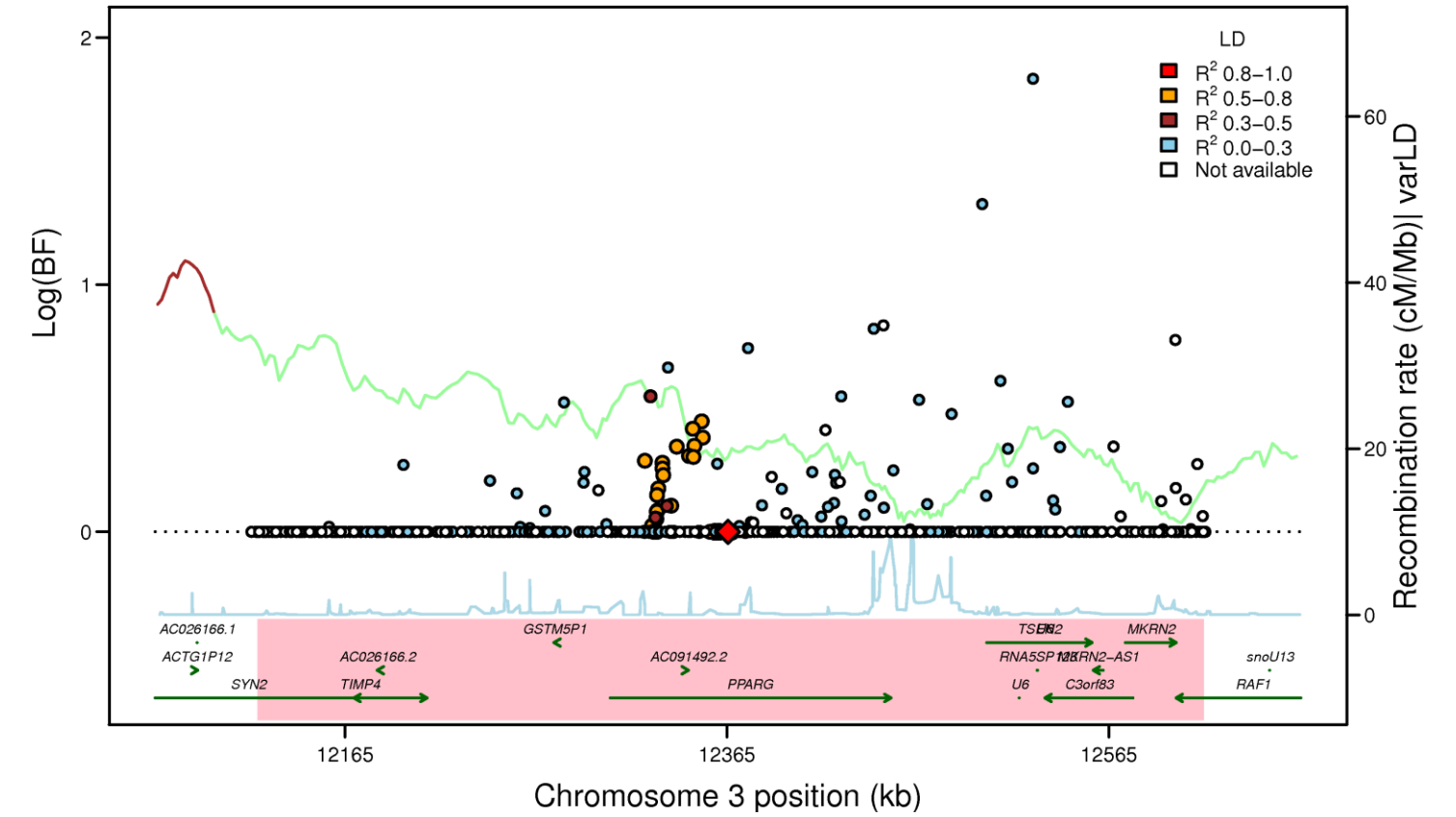


Figure S3W

PPARG: rs17036328 (FI EA_MANTRA, LD: HapMap2 CEU)



PPARG: rs17036328 (FI AA_MANTRA, LD: HapMap2 YRI)



PPARG: rs17036328 (FI TE_MANTRA, LD: HapMap2 YRI)

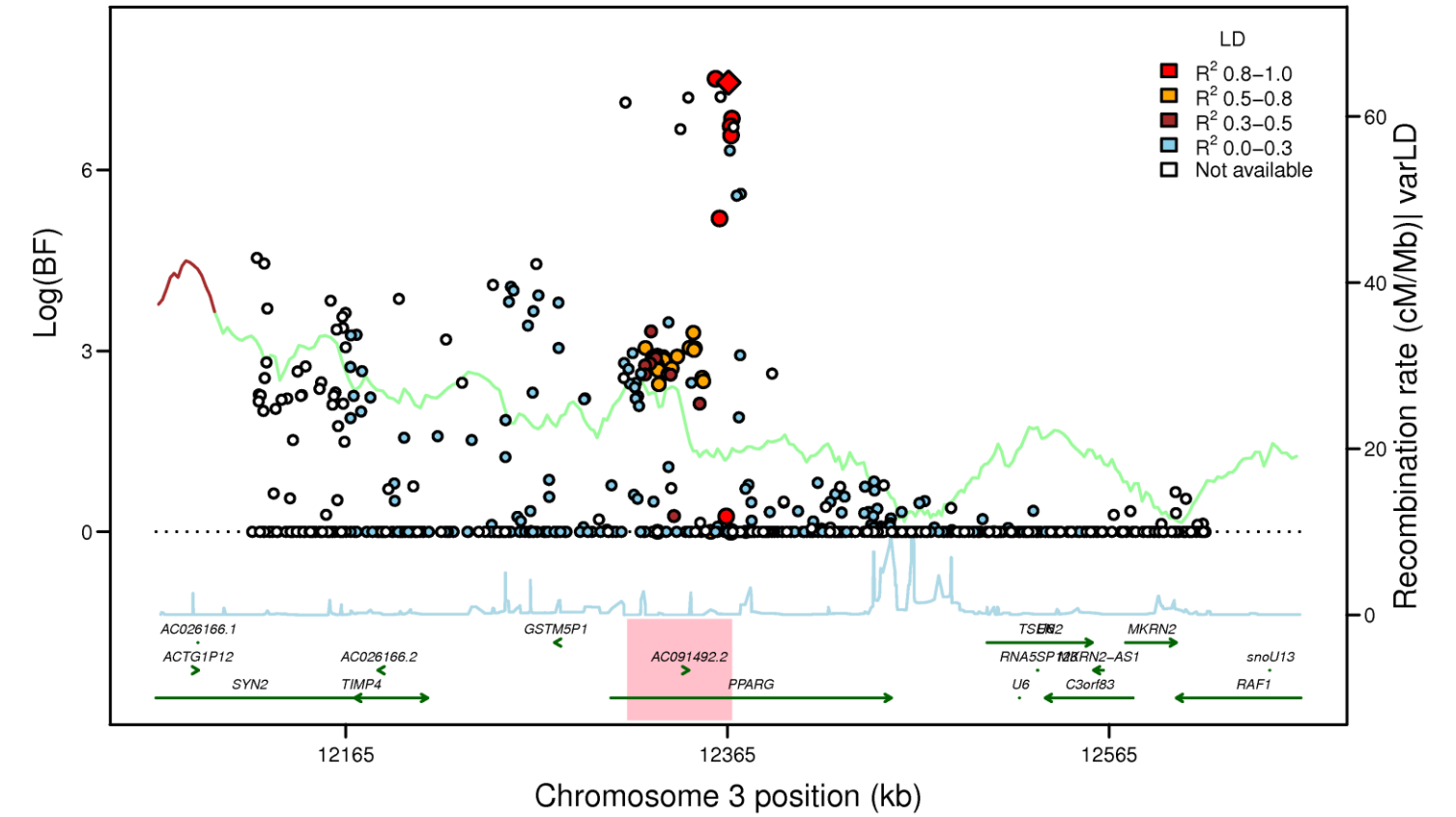


Figure S4. Regional association plots merged with data from RegulomeDB and Islet Regulome Browser at 14 FG and 9 FI loci with substantially narrowed credible sets after trans-ethnic analysis.

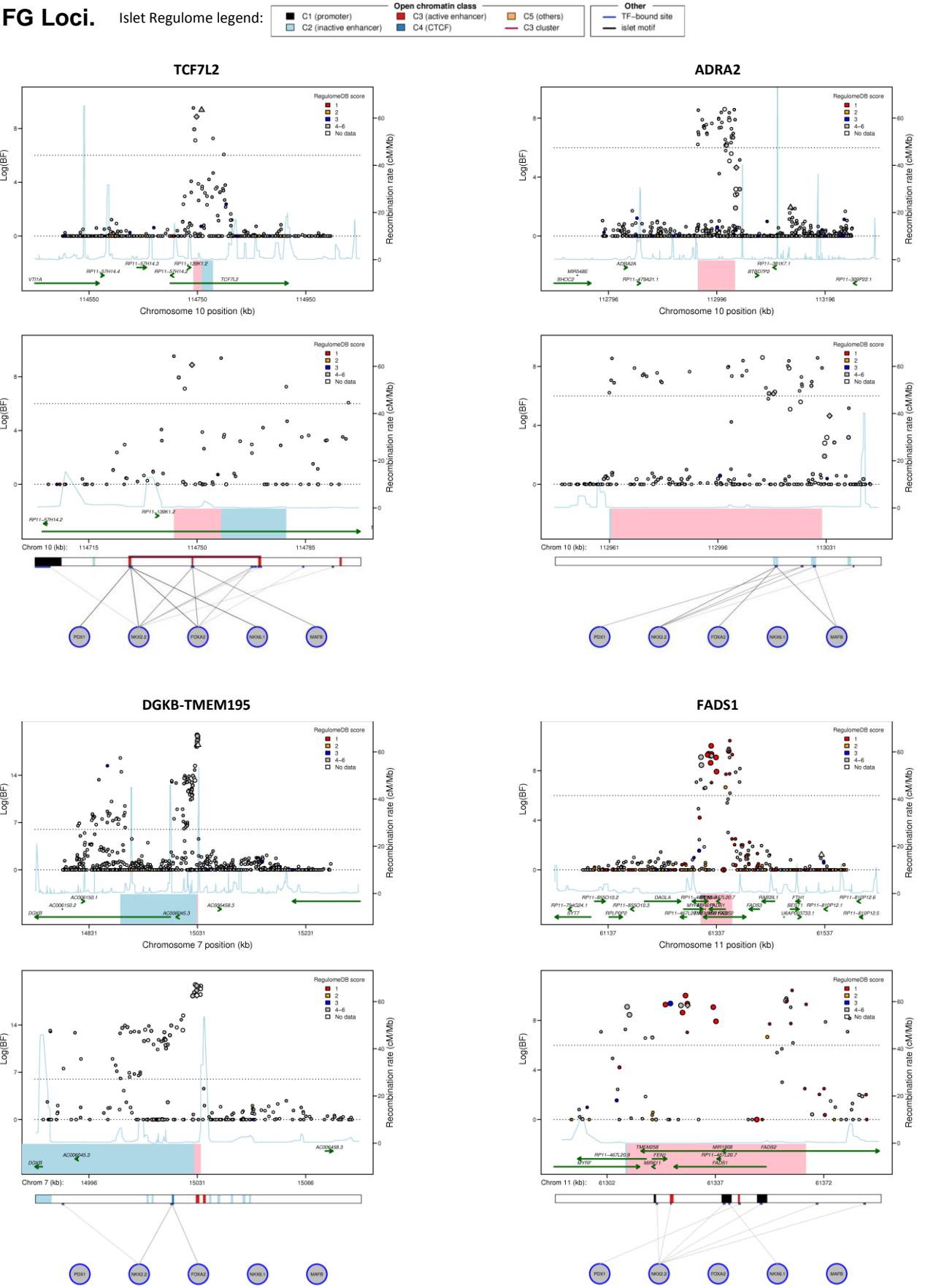


Figure S4, FG Loci continued.

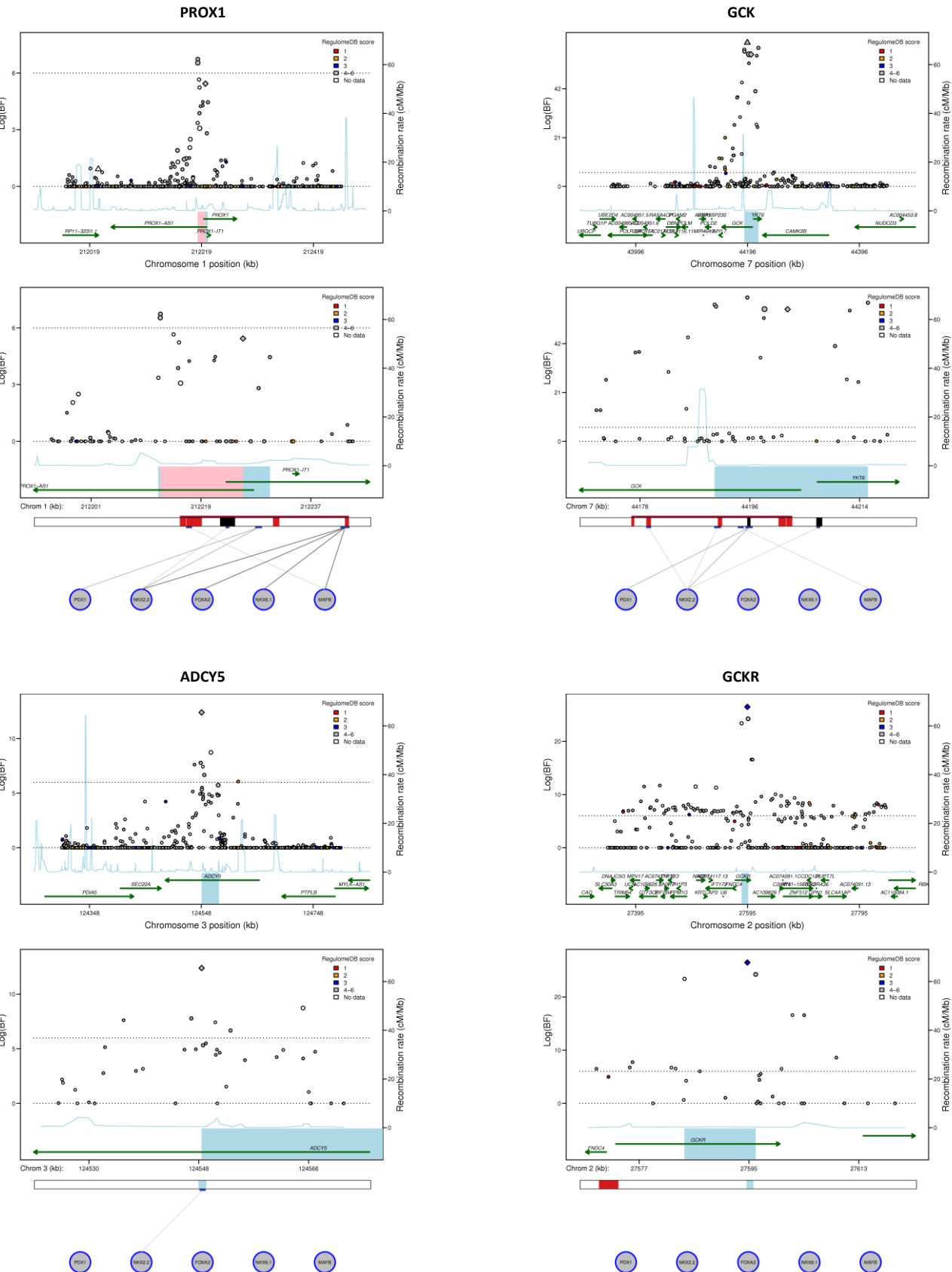
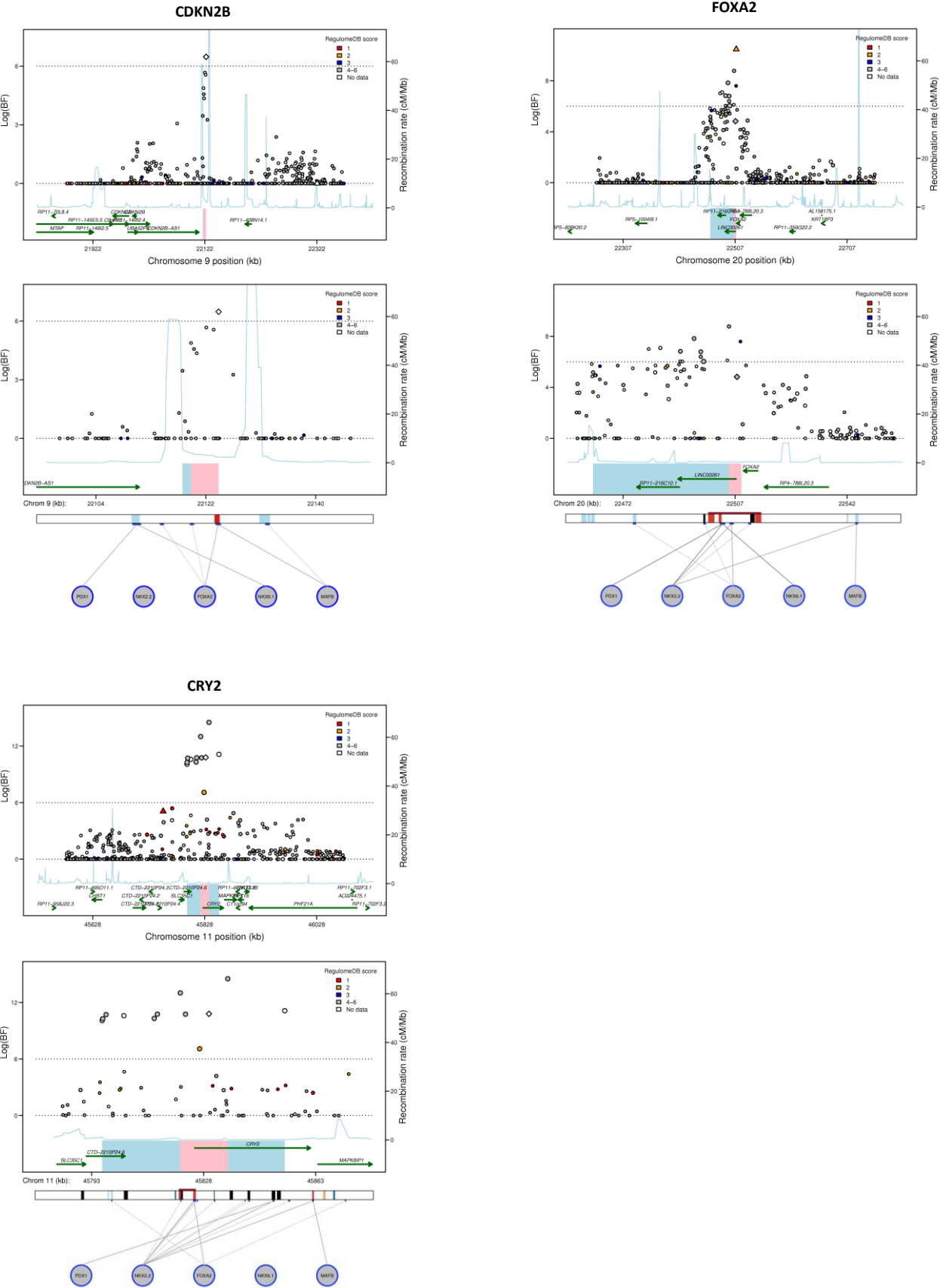
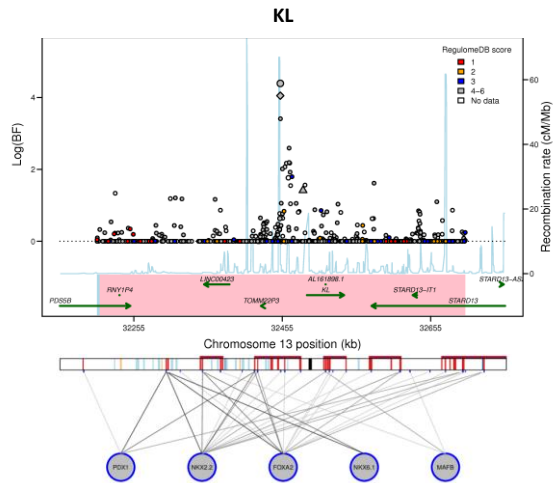
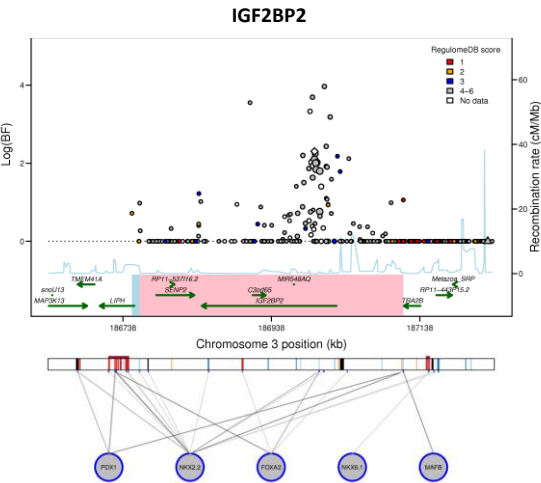
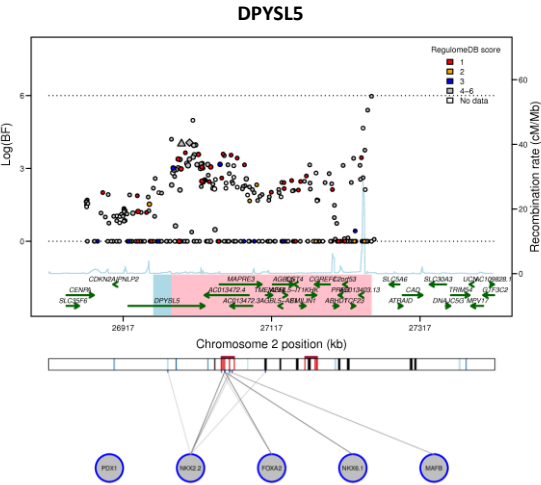


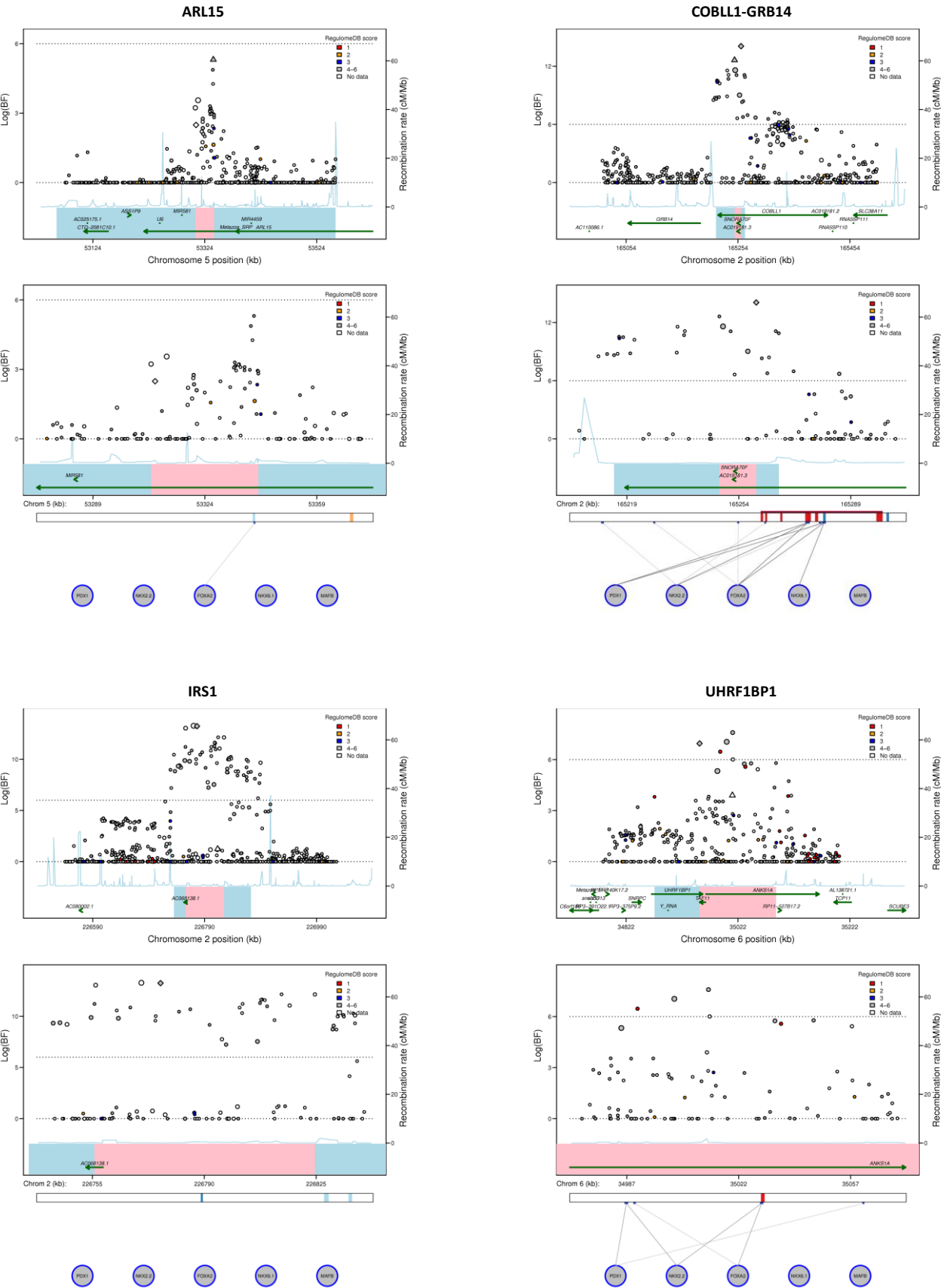
Figure S4, FG Loci continued.



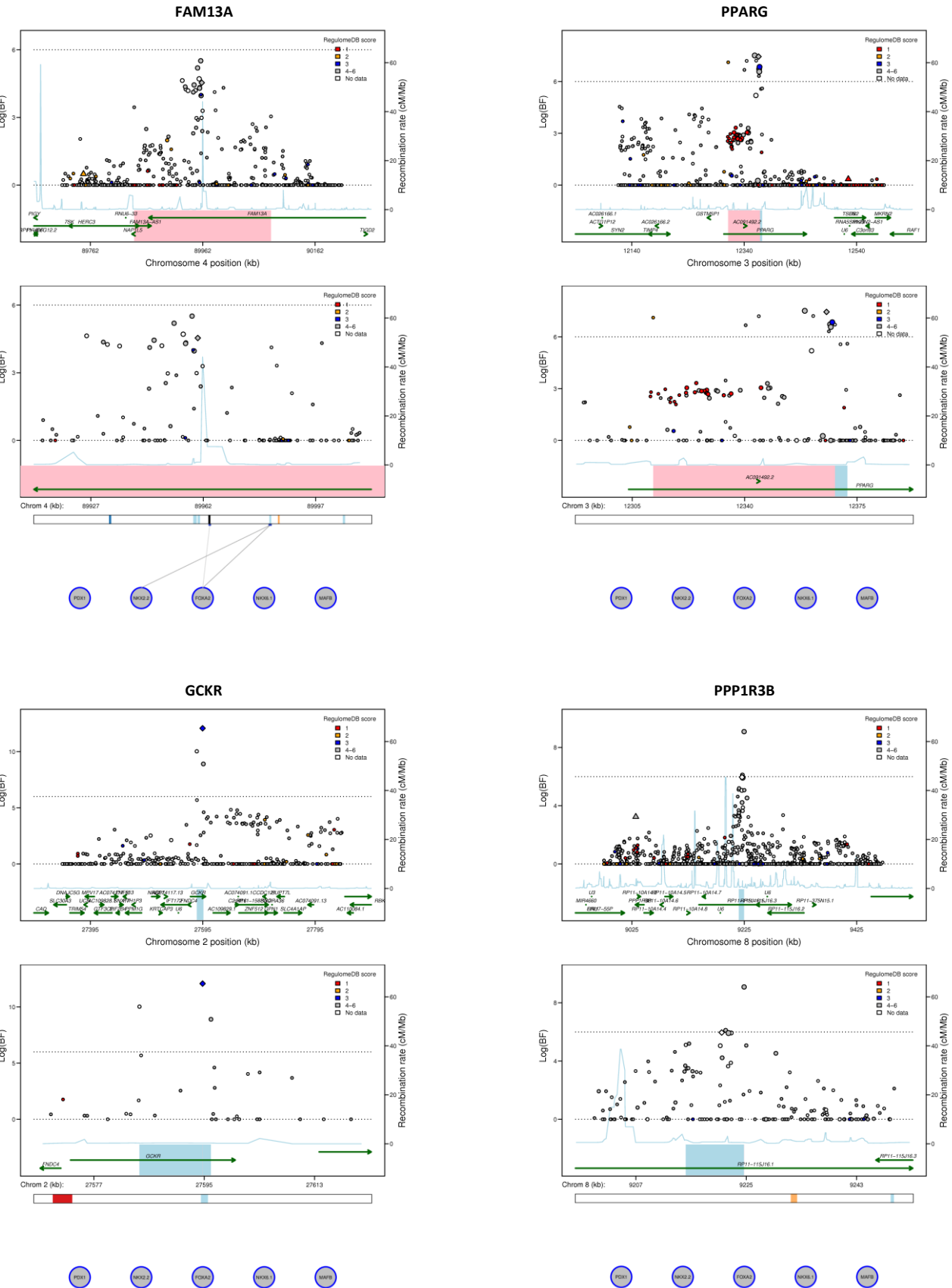
Supplemental Figure 4, FG Loci continued.



Supplemental Figure 4, FI Loci.



Supplemental Figure 4, FI Loci continued.



Supplemental Figure 4, FI Loci continued.

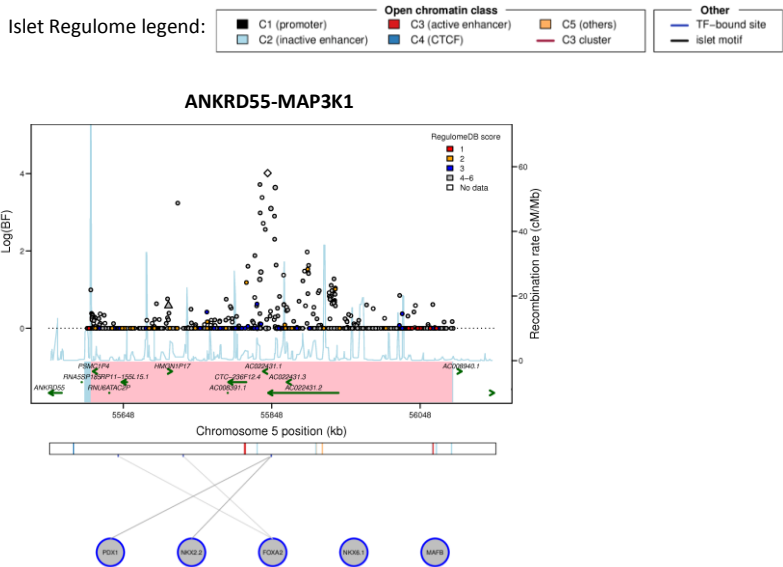


Figure S5

Previously identified EA snp with transferability from EA to AA, i.e $P < 0.05$ in AA and share the same trait-raising allele

Previously identified EA snp without evidence of transferability from EA to AA

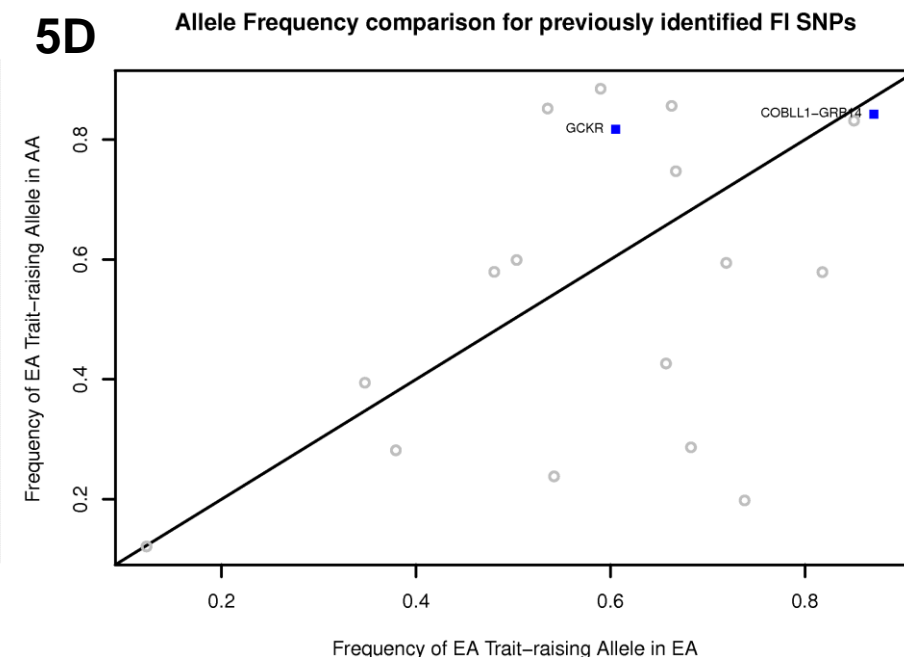
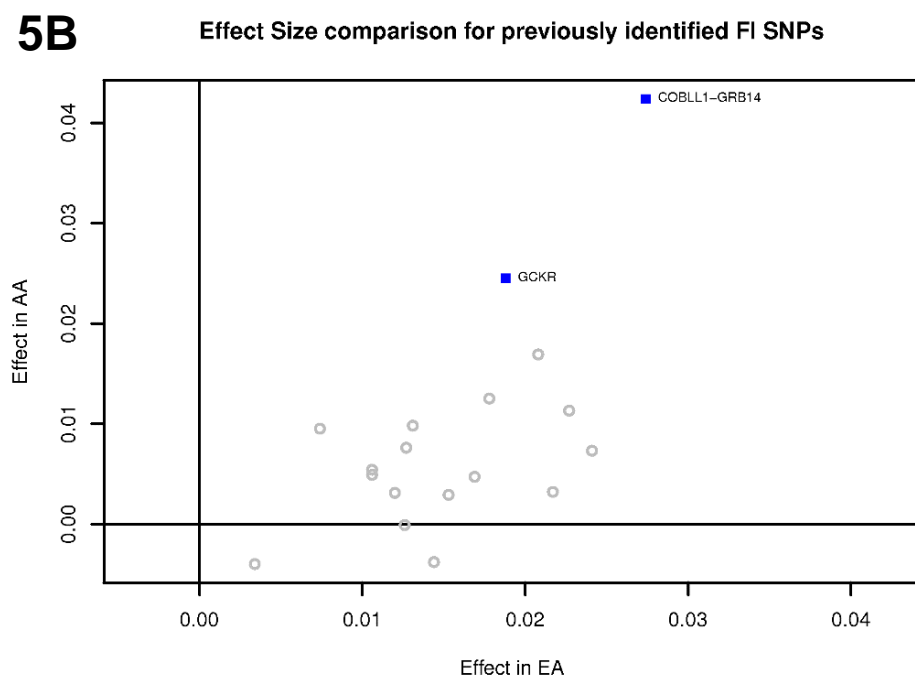
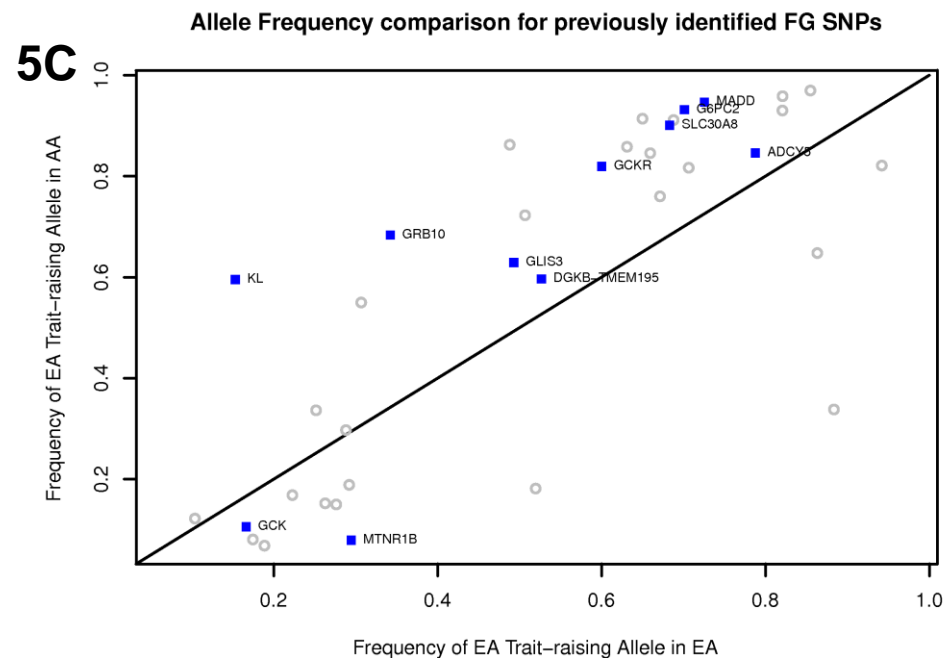
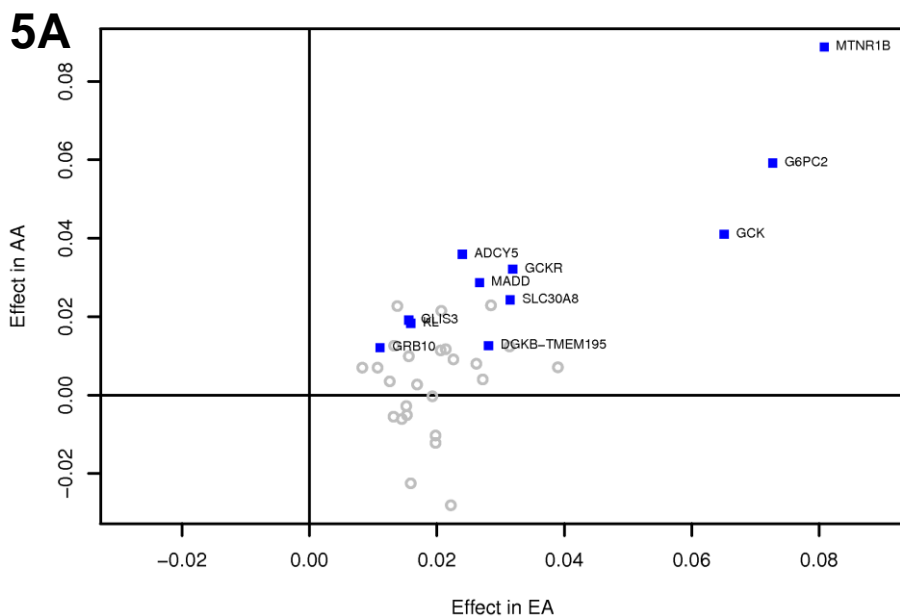


Figure S6A

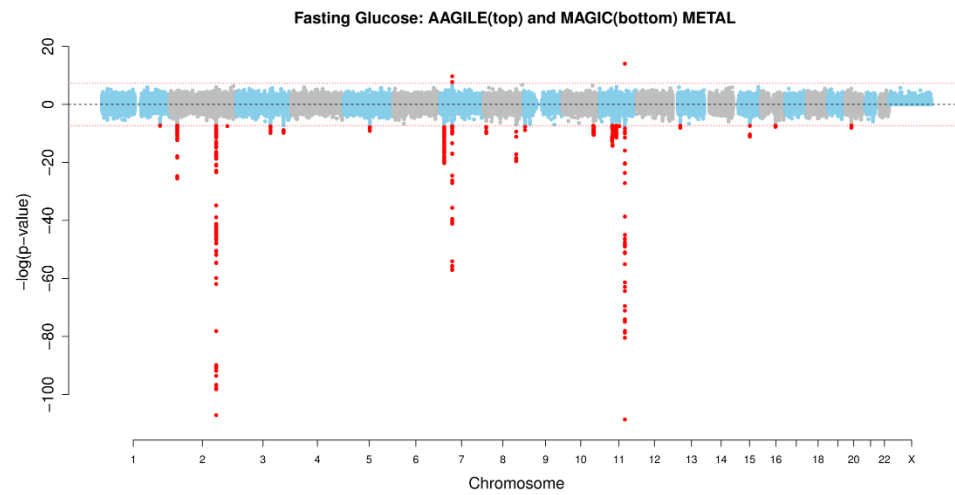


Figure S6B

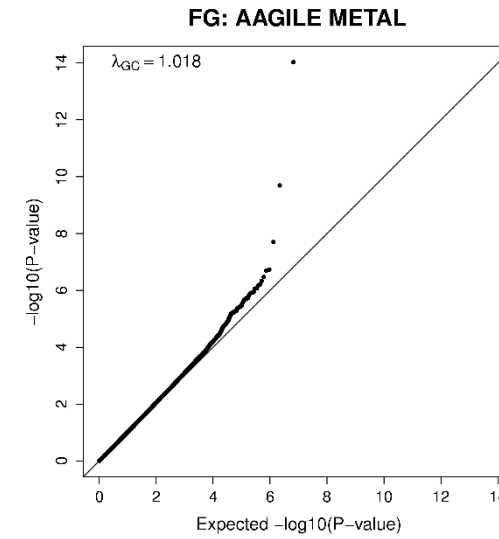


Figure S6C

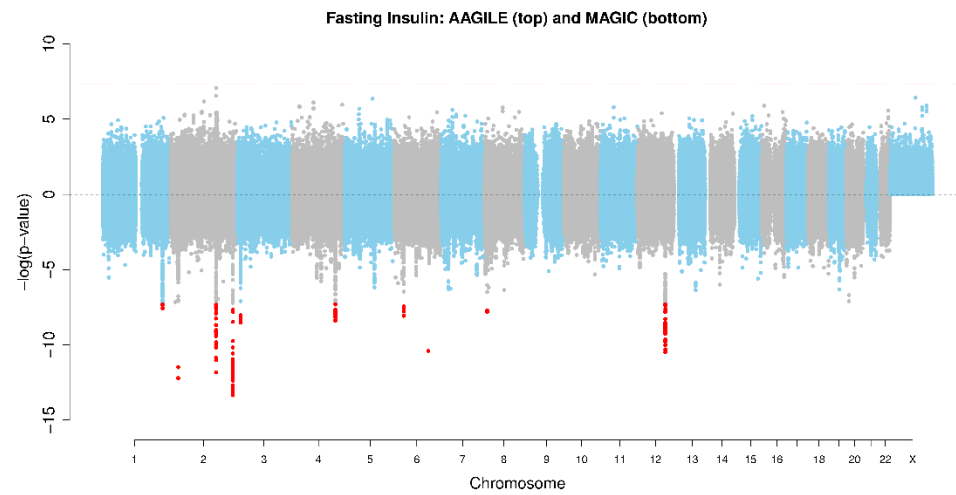


Figure S6D

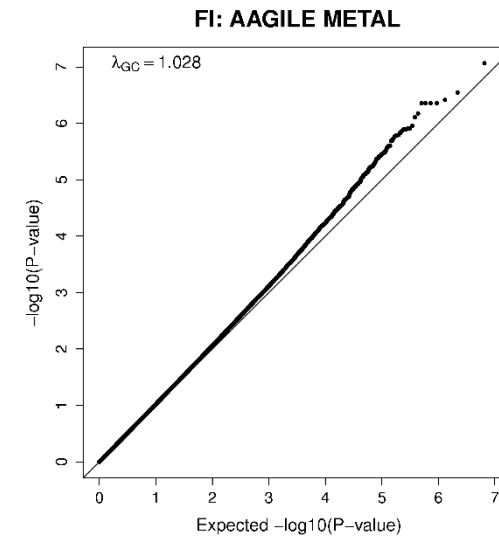


Figure S6E

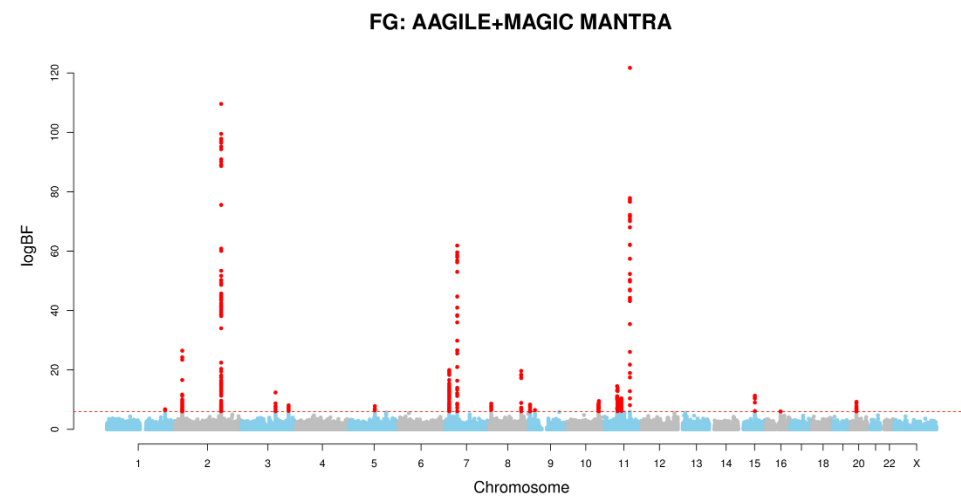


Figure S6F

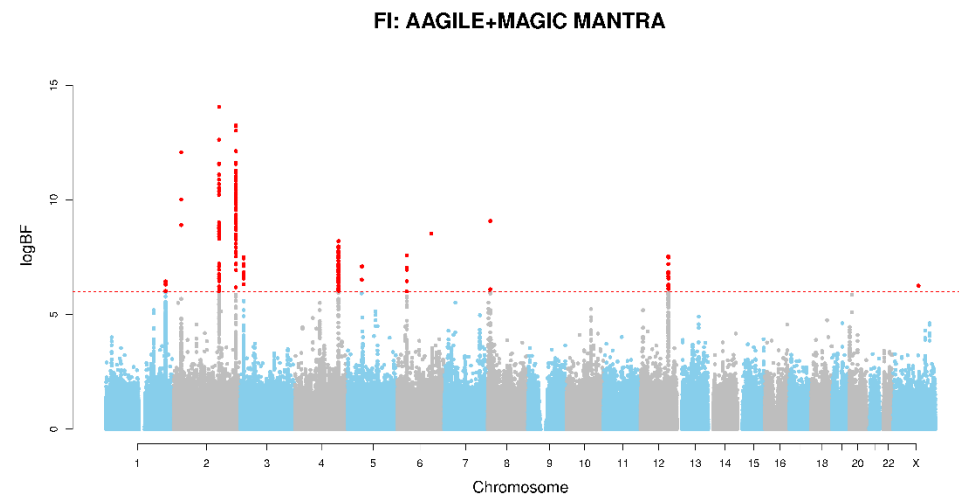


Figure S7

Figure S7A

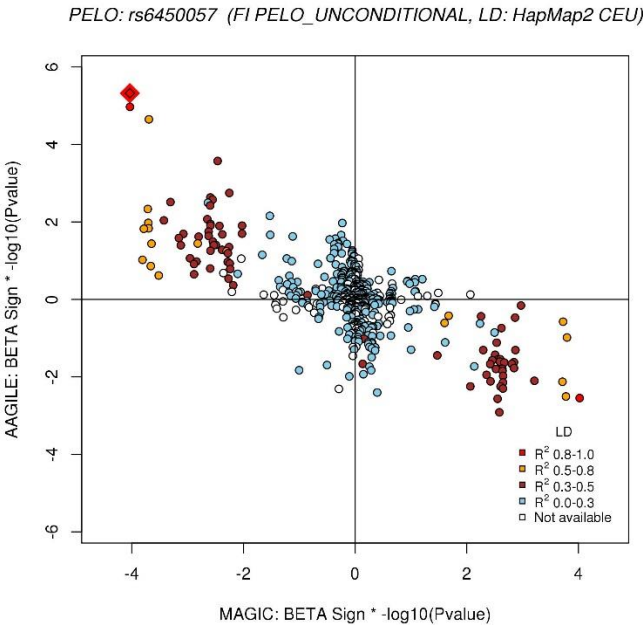


Figure S7B

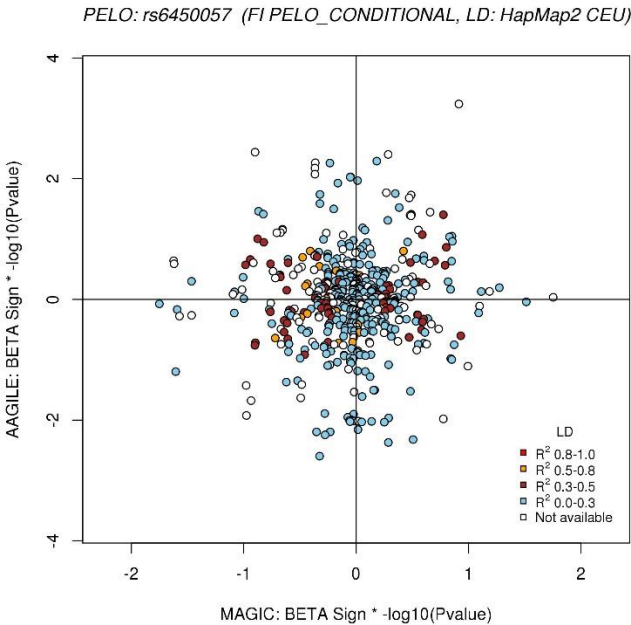


Figure S7C

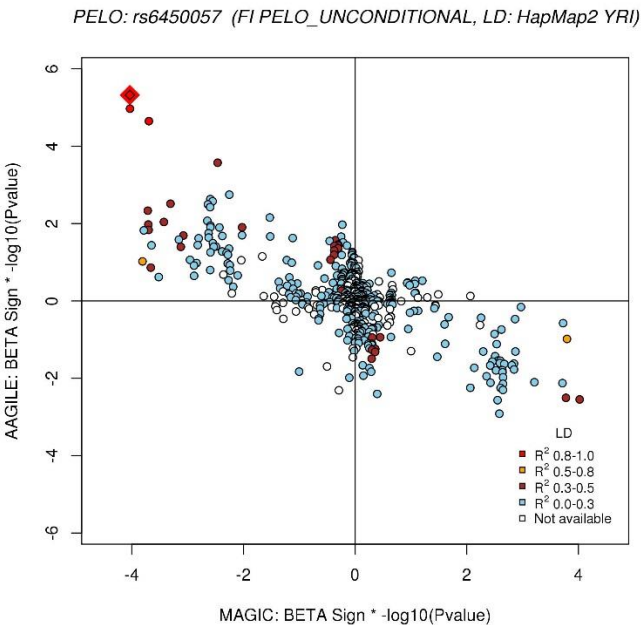
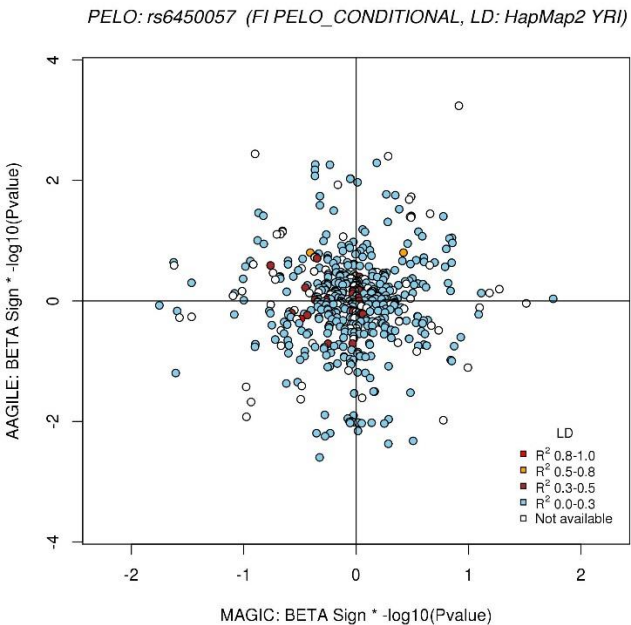


Figure S7D



Legend of Supplemental Figures

Figure S1. Schematic study diagram. 36 fasting glucose (FG) loci, 16 fasting insulin (FI) loci, and 2 loci associated with both FG and FI previously identified in European ancestry (EA) samples were fine-mapped by combining association statistics from EA and African ancestry (AA) samples using Meta-ANalysis of TRans-ethnic Association studies (MANTRA) software. Substantially reduced trans-ethnic credible sets were further examined for evidence of regulatory annotation or enrichment of regulatory marks. Known loci from EA samples were also analysed for transferability to AA samples, for evidence of independent signals in AA populations, and for evidence of selection. Novel FG- and FI-associated loci were identified in fixed effects GWAS meta-analysis in AA samples alone and in trans-ethnic analyses combining EA and AA samples. Two novel loci associated with FI and 24 loci known from EA samples were examined for association with other cardiometabolic traits.

Figure S2. Venn diagram of trans-ethnic analysis and transferability results. Venn diagram showing loci exhibiting transferability between EA and AA in brown, loci at which 99% credible set was reduced by at least 20% shown in blue, and overlapping loci in the central area.

Figure S3. Trans-ethnic fine-mapping of 22 loci (13 FG, 8 FI, and 1 both FG and FI) with greater than 20% reduction in the 99% credible set. Trans-ethnic analysis of glycemic quantitative loci provides narrowed intervals spanned by the 99% credible set. 500 kb regional association plots centered at the index SNP identified from EA samples at each locus. The X-axis denotes genomic position and the Y-axis denotes the log (Bayes factor), recombination rate and varLD information. The red diamond data point represents the index SNP within the region previously reported from the EA sample. The color of each data point indicates its LD value (r^2) with the index SNP based on HapMap 2 (YRI for AA results and CEU for EA results): white, r^2 not available; blue, $r^2=0.0-0.2$; brown, $r^2=0.2-0.5$; orange, $r^2=0.5-0.8$; red, $r^2=0.8-1.0$. The blue line represents the recombination rate. The green line shows the varLD score at each SNP and is highlighted with dark brown if the varLD score is $> 95^{\text{th}}$ percentile of the genome-wide varLD score, comparing LD information between YRI and CEU HapMap2 samples⁵². The interval spanned by the 99% credible set is highlighted in pink. For each locus, three figures were provided. **Panel A. Association results using EA samples. Panel B. Association results using AA samples. Panel C. Association results using both EA and AA samples.**

Figure S4. Overlay of regional association plots with regulatory annotation at 22 loci (13 FG, 8 FI, and 1 both FG and FI) with greater than 20% reduction in the 99% credible set. **Top panel:** 500 Kb genomic span showing the top SNP in EA (MAGIC) with a diamond, the top SNP in AA (AAGILE) with a triangle, the EA-only 99% credible set bounded by the blue and pink boxes, and the narrowed trans-ethnic 99% credible set indicated by the pink boxes. SNPs are colored according to score assigned in RegulomeDB with lower score corresponding to stronger level of evidence supporting regulatory function. **Lower panel (where shown):** A zoomed in region of the locus, showing either a 100 Kb or a 50 Kb genomic span. Again, the top SNP in EA (MAGIC) is represented by a diamond, SNPs are colored according to score assigned in RegulomeDB with lower score corresponding to stronger level of evidence supporting regulatory function, and the blue box indicates the span of the EA-only 99% credible set while the pink box indicates the narrowed trans-ethnic 99% credible set. Data from the Islet Regulome Browser for the genomic interval are shown below the regional association plots.

Figure S5. Concordance of effect size and Comparison of EA trait-raising allele Frequency in EA and AA. We show the concordance of effect (Figures S5A and S5B) and comparison of

frequency (**Figures S5C and S5D**) for each EA trait-raising allele between EA and AA samples. The blue rectangles represent the SNPs meeting SNP transferability criteria from EA to AA, i.e. association $P < 0.05$ in AA and sharing the trait-raising allele in EA and AA. Grey circles represent SNPs without evidence of SNP transferability. In **Figures S5A and S5B**, X-axis is the effect size in EA and Y-axis is the effect size in AA for the EA trait-raising allele. There is evidence of excess concordance of effect between EA and AA. Specifically, of 36 EA FG index SNPs, 28 SNPs share the same direction in AA (binomial test P of 5.96×10^{-4}), (**Figure S5A**); of 18 EA FI index SNPs, 14 SNPs share the same direction in AA (binomial test P of 1.544×10^{-2}), (**Figure S5B**). Also, for both traits, SNPs that meet the transferability criteria tended to have larger effect size of similar magnitudes in both the EA and AA samples than those not meeting criteria. In **Figures S5C and S5D**, X-axis is the frequency in EA and Y-axis is the frequency in AA for the EA trait-raising allele. There is wide variation in the frequency of the EA trait-raising allele between EA and AA; the majority of SNPs with locus transferability from EA to AA exhibit higher frequency of the EA trait-raising allele in AA than in EA.

Figure S6. Genome-wide association plots and quantile-quantile (QQ) plots for FG and FI. **Figures S6A and S6C** display the Miami plots of association, which mirror the results of AA (on the top) and EA (on the bottom). The X-axis is the chromosome and position and the Y-axis is the $-\log$ -scale of association P . **Figures S6B and S6D** are the QQ plots for FG and FI, respectively. Both associations of FG and FI are minimally inflated with lambda of 1.018 and 1.028, respectively. **Figures S6E and S6F** are the genome-wide association plots of trans-ethnic meta-analysis results for FG and FI, respectively. The X-axis is the chromosome and position and the Y-axis is the $-\log$ -scale of association P .

Figure S7. Conditional analysis at *PELO*/rs6450057. The product of the sign of the beta-coefficient for FI level and $-\log(P\text{-value})$ for each SNP residing $\pm 250\text{kb}$ of the top SNP, rs6450057, at the locus in EA samples (MAGIC) and in AA samples (AAGILE) plotted on the X- and Y-axis, respectively. **Figures S7A and 7C** show the comparison for unconditional association results with HapMap 2 CEU and YRI LD information, respectively. **Figures S7B and S7D** show the comparison for conditional association results with HapMap 2 CEU and YRI LD information, respectively. There is a clear pattern in the discordant directions of effect between EA and AA. However, after conditional analysis on the top SNP, this discordant pattern disappears, implying that the top SNP rs6450057 drives the original association signal.

Supplemental Tables

Table of Contents (All Tables are available in a separate file.)

Table S1. Cohort-specific characteristic information for all participating cohorts.

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Table S3. Annotation comparison of SNPs in trans-ethnic 99% credible set vs the SNPs in the credible set using European ancestry-only data but excluded after trans-ethnic analysis for the 9 FI loci with substantial reductions in credible set size.

Table S4. Annotation comparison of SNPs in trans-ethnic 99% credible set vs the SNPs in the credible set using European ancestry data only but excluded after trans-ethnic analysis for the 14 FG loci with substantial reductions in credible set size.

Table S5. Summary of credible set SNP annotation from HaploReg at 22 loci (13 FG, 8 FI, and 1 both FG and FI) with substantial 99% credible set reductions.

Table S6. Summary of manual annotation of genes, regulatory data, and evidence of expression at 22 loci (13 FG, 8 FI, and 1 both FG and FI) with substantial 99% credible set reductions.

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Table S9. Association results in the African ancestry samples for the most associated SNP within the interrogated region \pm 250kb of the European ancestry index SNP conditional on the European ancestry index SNP.

Table S10. Allele frequency difference, F_{st} s and iHSs in the African and European ancestry samples

Table S11. Associations between top FG and FI SNPs and diabetes and insulin resistance traits in an African ancestry sample

Table S12. Association results in the African ancestry samples, ranked according to priority tier and discovery P-value, for all 62 putative novel variants taken from discovery to replication analysis.

References

1. Manning, A.K. *et al.* A genome-wide approach accounting for body mass index identifies genetic variants influencing fasting glycemic traits and insulin resistance. *Nature genetics* **44**, 659-69 (2012).
2. Wang, Y.J. *et al.* The association of the vanin-1 N131S variant with blood pressure is mediated by endoplasmic reticulum-associated degradation and loss of function. *Plos Genetics* **10**, e1004641 (2014).
3. McCarty, C.A. *et al.* The eMERGE Network: a consortium of biorepositories linked to electronic medical records data for conducting genomic studies. *BMC medical genomics* **4**, 13 (2011).
4. Lettre, G. *et al.* Genome-wide association study of coronary heart disease and its risk factors in 8,090 African Americans: the NHLBI CARE Project. *Plos Genetics* **7**, e1001300 (2011).
5. Ng, M.C. *et al.* Meta-analysis of genome-wide association studies in African Americans provides insights into the genetic architecture of type 2 diabetes. *Plos Genetics* **10**, e1004517 (2014).
6. Monda, K.L. *et al.* A meta-analysis identifies new loci associated with body mass index in individuals of African ancestry. *Nature genetics* **45**, 690-6 (2013).
7. Liu, C.T. *et al.* Genome-wide association of body fat distribution in African ancestry populations suggests new loci. *Plos Genetics* **9**, e1003681 (2013).
8. Ward, L.D. & Kellis, M. HaploReg: a resource for exploring chromatin states, conservation, and regulatory motif alterations within sets of genetically linked variants. *Nucleic acids research* **40**, D930-4 (2012).